DuPont Haskell Laboratory
for Health and Environmental Sciences
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Newark, DE 19714-0050

MR# 302442

07 FEB -9 AM 10:55

February 8, 2007

Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
Washington, DC 20460

8EHQ-81-394

Dear 8(e) Coordinator:

8EHQ-0381-0394
Ammonium Perfluorooctanoate (APFO Linear)

This letter is to follow-up on our correspondence with the Agency of June 19, 2006 concerning a 28-day immunotoxicity study in male rats and mice with the above referenced substance.

Enclosed please find copies of the final reports.

Sincerely,

A. Michael Kaplan /clp

A. Michael Kaplan, Ph.D.
Director – Regulatory Affairs and Occupational Health

AMK: clp
(302) 366-5260

Enclosure (2): Ammonium Perfluorooctanoate: 28-Day Immunotoxicity Study in Male Rats; DuPont-18317

Ammonium Perfluorooctanoate: 28-Day Immunotoxicity Study in Male Mice; DuPont-18318

CONTAINS NO CBI

mr#
302442

TRADE SECRET

Study Title

Ammonium Perfluorooctanoate: 28-Day Immunotoxicity Study in Male Rats

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.7800 (1998)

AUTHOR: Denise Hoban, B.A, MLT (ASCP)

STUDY COMPLETED ON: February 1, 2007

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
Haskell[SM] Laboratory for Health and Environmental Sciences
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Newark, Delaware 19714
U.S.A.

Exygen Research
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Experimental Pathology Laboratories, Inc.
615 Davis Drive, Suite 500
Durham, North Carolina 27713
U.S.A.

Laboratory for Advanced Electron and Light Optical Methods
College of Veterinary Medicine
North Carolina State University
4700 Hillsborough Street
Raleigh, North Carolina 27606
U.S.A.

LABORATORY PROJECT ID: DuPont-18317

CONTAINS NO CBI

WORK REQUEST NUMBER: 16160

SERVICE CODE NUMBER: 1545

SPONSOR: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

PAGE RESERVED

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA FIFRA (40 CFR part 160) Good Laboratory Practice Standards, which are compatible with current OECD and MAFF (Japan) Good Laboratory Practices, except for the item documented below. The item listed does not impact the validity of the study.

A non-GLP characterization was performed prior to the initiation of this study. The accuracy of the composition at the concentrations documented in this report is considered sufficient for the purpose of this study and is based on the process chemistry provided by the sponsor. GLP characterization was performed concurrently during the course of the study.

Applicant / Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Director: Denise Hoban 01 Feb 2007
Denise Hoban, B.A, MLT (ASCP) Date
Staff Medical Technologist and Supervisor

Applicant / Sponsor: _____ _____
DuPont Representative Date

QUALITY ASSURANCE STATEMENT

Work Request Number: 16160
Study Code Number: 1545

Phase Audited	*Audit Dates*	*Date Reported to Study Director*	*Date Reported to Management*
Protocol:	October 17, 2005	October 17, 2005	October 17, 2005
Conduct:	November 11, 2005	November 11, 2005	November 11, 2005
	November 14, 2005	November 14, 2005	November 14, 2005
	May 30, 2006*	October 31, 2006*	November 2, 2006*
	June 14, 2006*	October 31, 2006*	November 2, 2006*
	June 27, 2006*	October 31, 2006*	November 2, 2006*
	October 25, 2006*	October 31, 2006*	November 2, 2006*
Report/Records:	February 2, 7, 2006	February 7, 2006	February 8, 2006
	August 10, 11, 14-18, 2006	August 18, 2006	September 11, 2006
	November 13-14, 2006	November 14, 2006	December 12, 2006

* EPL QA Dates

Reported by: Joseph C Hamill 01-Feb-2007
Joseph C. Hamill
Quality Assurance Auditor
Date

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

Analytical Evaluation by: _____ 01-Feb-2007
Z. Amanda Shen, Ph.D.
Research Chemist
Date

Clinical Pathology Evaluation by: _____ 01-Feb-2007
Nancy E. Everds, D.V.M., Diplomate A.C.V.P.
Principal Research Clinical Pathologist and Manager
Date

Anatomic Pathology Evaluation by: _____ 01-Feb-2007
Greg P. Sykes, V.M.D., Diplomate A.C.V.P.,
A.C.L.A.M., A.B.T.®
Veterinary Pathologist
Date

Anatomic Pathology Evaluation Peer Review by: _____ 01-Feb-2007
Steven R. Frame, D.V.M., Ph.D., Diplomate A.C.V.P.
Research Fellow and Manager
Date

Reviewed and Approved by: _____ 01-Feb-2007
Scott E. Loveless, Ph.D.
Research Manager and Director
Date

Issued by Study Director: _____ 01Feb2007
Denise Hoban, B.A, MLT (ASCP)
Staff Medical Technologist and Supervisor
Date

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STUDY INFORMATION

Substance Tested:
- Ammonium Perfluorooctanoate [AFPO (linear)]
- 3825-26-1 (CAS Number)

Haskell Number: 27308

Composition: Ammonium Perfluorooctanoate Solution 19.5% in water

Purity: 19.5%

Physical Characteristics: White to slightly opaque liquid

Stability: The test substance was stable under the conditions of the study based on analytical results.

Study Initiated/Completed: October 14, 2005 / (see report cover page)

Experimental Start/Termination: October 16, 2005 / February 1, 2007

SUMMARY

The purpose of this study was to evaluate the potential of ammonium perfluorooctanoate [APFO (linear)] to suppress the primary humoral immune response following exposure via oral gavage for up to 28 consecutive days. Groups of 10 male rats each were administered the test substance at daily levels of 0, 0.3, 1, 10, 30, and 30/0 mg/kg. The group designated 30/0 mg/kg was included to assess potential reversibility/recovery and was therefore administered the test substance for 22 consecutive days followed by 6 consecutive days of vehicle (water) administration. Body weights, food consumption measurements, and clinical observations were recorded during the in-life period. Prior to sacrifice, the immune system was stimulated by injecting sheep red blood cells (SRBC) on test day 22 and blood samples were collected from each rat on test day 29. The serum samples were assayed for their concentration of SRBC-specific IgM antibodies to provide a quantitative assessment of humoral immune response. Serum from animals dosed with cyclophosphamide, a positive control immunosuppressive agent, were analyzed concurrently to provide confirmation that the assay performance was acceptable for detection of immunosuppression. Clinical pathology data were collected at day 29 to assess effects on hematology and clinical chemistry. At sacrifice, each animal was examined grossly and selected organs were weighed (brain, spleen, and thymus); selected tissues (as outlined in the methods section) were retained and examined histologically. Thymus and spleen cells were manually counted from single-cell suspensions prepared from the collected tissue.

Samples of the dosing formulations were chemically analyzed and the results indicated that the test substance was at the targeted concentrations, homogeneously mixed, and stable under the conditions of the study.

Test substance-related toxicity was observed during the in-life portion of the study at 1 mg/kg and higher. Adverse reductions in body weights, weight changes, food consumption, and food efficiency occurred at 10 mg/kg and higher; at 30 and 30/0 mg/kg, these reductions were accompanied by low incidences of clinical observations indicative of toxicity. Effects on body weight and food consumption parameters were detected at 1 mg/kg, but these reductions were not considered adverse. There were no test substance-related effects observed at 0.3 mg/kg during the in-life portion of the study.

Rats dosed with ≥0.3 mg/kg had decreased serum total, HDL, and non-HDL cholesterol, and decreased triglycerides. Rats dosed with ≥1 mg/kg had increased microscopic red cell morphologic changes and hemolyzed serum. Rats dosed with ≥10 mg/kg had decreased hemoglobin, hematocrit, mean cell volumes, and mean cell hemoglobin concentrations; increased reticulocyte counts and red cell distribution width, increased total white blood cell, neutrophil, monocyte, and LUC counts; increased serum albumin and decreased serum globulin concentrations; and increased serum corticosterone concentrations. Rats in the 30/0 mg/kg group had more pronounced red cell mass effects and red cell morphologic changes compared to those dosed with 30 mg/kg for 29 days. Parameters with complete recovery in rats dosed with 30/0 mg/kg were serum total, HDL, and non-HDL cholesterol, globulin, and corticosterone concentrations.

There was a test substance-related decrease in final body weights and increase in liver weights. Mean final body weights were decreased at dose levels ≥10 mg/kg of the test substance. Mean liver weight parameters were increased at dose levels ≥0.3 mg/kg. At the terminal sacrifice, test substance-related gross observations were limited to discoloration of the liver in a few rats at doses ≥10 mg/kg. Microscopic examination of the liver demonstrated minimal to mild hepatocellular hypertrophy at 0.3 and 1 mg/kg and moderate hepatocellular hypertrophy at ≥10 mg/kg. Microscopic examination of lymphohematopoietic organs (spleen, thymus, bone marrow, lymph nodes) revealed increased hematopoiesis in the spleen of rats dosed with 30/0 mg/kg.

No test substance-related evidence of immunosuppression was observed in male rats at any concentration tested; the IgM titers were generally comparable across all groups.

No significant changes in total spleen cell or thymocyte number compared to control rats were noted in any animals treated with any dose of APFO.

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for APFO for systemic toxicity in male rats was less than 0.3 mg/kg, whereas the NOAEL for immunotoxicity was 30 mg/kg.

INTRODUCTION

The primary objective of this study was to evaluate the potential of ammonium perfluorooctanoate [APFO (linear)] to suppress the primary humoral immune response to sheep red blood cells (SRBC) when administered by oral gavage to male rats for at least 28 days. Additional endpoints of toxicity were also evaluated. The oral route of administration was selected because it is a potential route of human exposure.

Ammonium perfluorooctanoate (APFO; FC-143, C_8; $C_7F_{15}COO^-NH_4^+$; CAS Registry number 3825-26-1) is a surfactant used as a processing aid in the production of fluoropolymers. Perfluorooctanoate (PFOA; $C_7F_{15}COO^-$), the dissociation product of APFO, is not metabolized[1] and has been identified in blood samples from exposed workers and the general population.[2,3,4]

PFOA has been reported to inhibit the ability of mice to make antibodies to a T-cell dependent antigen.[5] The reported study employed a single 0.02% PFOA in chow (approximately 30 mg/kg) for 16 days. In order to better characterize the immune response following exposure to this material, APFO was administered by oral gavage using a broad range of doses.

Dosages for this study were selected based on results of a 14-day oral gavage study in male rats and mice.[6]

STUDY DESIGN

A. Design Concentrations

Group	Number/ Group	Daily Dosage (mg/kg)[a]	Dose Solution Concentration (mg/mL)[b]
I	10	0 (Control)	0
III	10	0.3	0.03
V	10	1	0.1
VII	10	10	1
IX	10	30	3
XI	10	30/0[c]	3

a Weight of test substance/kg or animal body weight.
b Solutions were adjusted for purity (19.5%).
c This group (XI) was dosed with 30 mg/kg of test substance through test day 22. Following injection of SRBC on test day 23, group XI was dosed with NANOpure® water, at a volume of 10 mL/kg of body weight, until sacrifice.

B. Study Overview

Study Parameters	Frequency
Body Weight	Day 0, 3, 6, and daily thereafter
Food Consumption	Weekly
Daily Animal Health Observation	Twice daily
General Clinical Observation[a]	Day 0 and weekly thereafter
Detailed Clinical Observation	At each weighing
SRBC Injection	Prior to dosing (test day 23)
Clinical Pathology Evaluation	Test day 29
Serum Collection for Antibody Determination	At sacrifice (test day 29)
Anatomic Pathology Evaluation	Test day 29

a A check for acute signs of toxicity was conducted approximately 2 hours post-dosing.

MATERIALS AND METHODS

A. Test Guidelines

The study design complied with the following test guidelines:

- U.S. EPA, OPPTS 870.7800: Immunotoxicity, *Health Effects Test Guidelines* (1998)

B. Test Substance

(Appendix A)

APFO (linear), was supplied by the sponsor as a white to slightly opaque liquid in a 19.5% aqueous solution. The bulk test substance was used within the period of approved use as defined by the expiration date listed on the Certificate of Analysis (COA) that is provided in Appendix A. No evidence of instability, such as a change in color or physical state, was observed.

C. Test System

On October 6, 2005, 66 male Crl:CD(SD) rats, with an assigned birth date of August 22, 2005, were received from Charles River Laboratories, Raleigh, North Carolina.

The Crl:CD(SD) rat was selected based on consistently acceptable health status and on extensive experience with this strain at Haskell Laboratory. By utilizing the Crl:CD(SD) rat, immunotoxicity studies can be conducted in the same strain that is used for other toxicology studies.

D. Animal Husbandry

1. Housing

All animals were housed singly in stainless steel, wire-mesh cages suspended above cage boards.

2. Environmental Conditions

Animal rooms were maintained at a temperature of 18-26°C and a relative humidity of 30-70%. Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle. Excursions outside of these ranges were of insufficient magnitude and/or duration to have adversely affected the validity of the study.

3. Feed and Water

All rats were provided tap water *ad libitum*. All rats were fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 *ad libitum*.

4. Animal Health and Environmental Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

E. Pretest Period

Upon arrival at Haskell Laboratory, all rats were housed in quarantine. The rats were:

- quarantined for 6 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.

- observed with respect to weight gain and any gross signs of disease or injury.

The rats were released from quarantine by the laboratory animal veterinarian or designee on the bases of acceptable body weights and clinical signs of all rats.

F. Assignment to Groups

Rats, selected on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury, were distributed by computerized, stratified randomization into study groups as designated in the Study Design, so that there were no statistically significant differences among group body weight means within a sex. The weight variation of selected rats did not exceed ± 20% of the mean weight for each sex.

At grouping, each rat was assigned an animal number/cage identification number. The animal number/cage identification number were tattooed on the tail of each rat and included on the cage label.

At study start (test day 0) the rats were 8 weeks of age.

G. Dose Formulation Preparation and Administration

The dosing solutions were prepared in NANOpure® water. The formulations were adjusted based on the percentage of APFO in the bulk test substance to achieve the desired concentrations. Dosing formulations were prepared on a daily basis.

Animals were dosed daily at approximately the same time (± 2 hours) by intragastric intubation at a dose volume of 10 mL/kg body weight for at least 28 consecutive days; individual dose volumes were calculated based on the most recently collected body weight data. Control rats were similarly dosed with NANOpure® water at a volume of 10 mL/kg of body weight. The 30/0 mg/kg group (XI) was dosed with 30 mg/kg of test substance through test day 22. Following injection of SRBC on test day 23, group XI was dosed with NANOpure® water at a volume of 10 mL/kg of body weight until sacrifice.

One rat from group XI (1109) was not dosed on test days 6 through 8 due to a decrease in body weight gain. Once body weight increases were observed for this rat, dosing resumed.

H. Dose Formulation Sampling and Analysis

1. Recovery Sample Analysis

Concurrent with dosing formulation analyses, recovery of APFO from spiked NANOpure® water was tested at the low level (approximately 0.03 mg/mL), the middle levels (approximately 0.1 and 1 mg/mL), and the high level (approximately 3 mg/mL) to confirm the analytical method. A stock solution of APFO was prepared in NANOpure® water. For all concentration levels, an appropriate aliquot of the stock solution was used to make the spiked solution upon further dilution with NANOpure® water. These spiked recovery samples were then processed and analyzed in the same manner as the dosing samples at similar concentrations.

2. Dosing Solution Treatment

Each dosing sample (1 mL) was initially diluted with NANOpure® water to a nominal concentration of 0.3, 1, 10, and 30 ppm APFO for the 0.03, 0.1, 1, and 3 mg/mL dosing samples, respectively. The samples were further diluted to a final expected concentration of 0.03 ppm with NANOpure® water for analysis. The 0 mg/mL sample followed the 0.03 mg/mL sample dilutions. Before the final dilution, the internal standard (1, 2-di-13C PFOA) was added to each sample to give an equivalent final concentration of the internal standard in all dosing samples; the 0.1, 1, and 3 mg/mL samples were matrix corrected with the initial diluted solution of the control sample.

3. Chromatographic Conditions

LC Parameters

Instrument: Agilent (Hewlett-Packard) 1100 liquid chromatograph
Column: Zorbax® RX-C8, 2.1 x 150 mm, 5 µm
Flow Rate: 0.4 mL/min
Oven Temperature: 35°C
Injection Volume: 20 µL
Mobile Phase: A) 0.15% Acetic acid in NANOpure® water
B) Acetonitrile
Gradient:

Time (min)	% Acetonitrile
0	5
0.9	5
1.0	80
5.0	80
5.1	5
7.0	5

MS Parameters

Instrument: Waters (Micromass) Quattro Micro
Ionization Mode: Electrospray (ESI), negative ion
Capillary Voltage: 2.7 kV
Cone Voltage: 15 V
Source Temperature: 120°C
Desolvation Temperature: 350°C
Scan Function: PFOA: 413 m/z (parent) to 369 m/z (daughter)
1, 2-di-13C PFOA: 415 m/z (parent) to 370 m/z (daughter)

4. Calibration and Quantitation

The analytical reference of APFO (H-22703-376, 100%) was used for quantitation of this study. A stock solution was prepared in NANOpure® water. This stock solution was mixed to ensure that all material was dissolved in solution. Before analysis, appropriate aliquots of the stock solution were diluted with NANOpure® water to make calibration standards that bracketed the target concentration of the diluted dosing samples after matrix correction with the initial diluted solution of the control sample. Before these aliquots were brought to the final volume, an

appropriate amount of 1, 2-di-13C PFOA internal standard was added to give an equivalent final concentration of the internal standard in all standard solutions.

The 369 m/z daughter ion of PFOA dissociated from APFO measured by LC/MS/MS was used against the 370 m/z daughter ion of 1, 2-di-13C PFOA internal standard to determine the concentrations of the dosing samples. Peak area ratios (369 m/z peak versus 370 m/z peak) of these standards were used to construct a calibration curve by least square regression (see Figure 1 for a representative calibration curve). Measured concentrations for dosing solutions were determined by applying the peak area ratios from replicate injections of each sample to the calibration curve.

Concentration verification of APFO in dosing samples was evaluated by the mean result of the duplicate analyses for each respective dosing level.

Uniformity of mixing of APFO in dosing samples was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentration in the duplicate analyses of the concentration verification samples. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution.

Stability of APFO in dosing samples was evaluated by using the mean result of the duplicate concentration verification analyses as the baseline for comparing the corresponding stability results.

I. Body Weights

During the test period, all rats were weighed on test days 0, 3, 6, and daily thereafter.

J. Food Consumption and Food Efficiency

During the test period, the amount of food consumed by each rat over the weighing interval was determined by weighing each feeder at the beginning and end of the interval and subtracting the final weight and the amount of spillage from the feeder during the interval from the initial weight. From these measurements, mean daily food consumption over the interval was determined. From the food consumption and body weight data, the mean daily food efficiency of test substance was calculated for each animal.

K. Clinical Observations

1. Daily Animal Health Observations

Cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats were conducted at least twice daily throughout the study. Abnormal behavior/appearance was recorded by exception.

2. General Clinical Observations

An additional cage-site evaluation was conducted approximately 2 hours after dosing to detect acute clinical signs of systemic toxicity.

3. Detailed Clinical Observations

At every weighing, each rat was individually handled and examined for abnormal behavior and appearance. Detailed clinical observations in a standardized arena were also evaluated on all rats. The detailed clinical observations included (but were not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior. Any abnormal clinical signs noted were recorded.

L. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all animals approximately 29 days after initiation of the study. These animals were fasted after 3 p.m. for at least 15 hours. Blood samples for hematology measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for clinical chemistry and humoral immune system evaluations were collected at sacrifice from the abdominal *vena cava* of each animal while the animal was under carbon dioxide anesthesia. Bone marrow smears were prepared at sacrifice from all surviving animals. Bone marrow smears were stained with Wright-Giemsa stain, but analysis was not necessary to support experimental findings. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. All blood samples were evaluated for quality by visual examination. Results were maintained in the study records and reported only if the sample was analyzed.

1. Hematology

Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-Giemsa-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology.

The following parameters were determined:

red blood cell count
hemoglobin
hematocrit
mean corpuscular (cell) volume
mean corpuscular (cell) hemoglobin
mean corpuscular (cell) hemoglobin concentration
red cell distribution width
absolute reticulocyte count
platelet count
white blood cell count
differential white blood cell count
microscopic blood smear examination

2. Clinical Chemistry

Routine serum clinical chemistry parameters were determined on an Olympus® AU640 clinical chemistry analyzer. Serum corticosterone was measured using a commercial RIA assay (Diagnostic Products Corporation, Los Angeles, CA; Catalog #TKRC1). Corticosterone concentrations were determined according to the manufacturer's recommended procedure (aspirating aqueous contents of the assay tube rather than decanting). If necessary, the standard curve was extended at the low end of the range by including standards of 5 and 10 ng/mL.

The following parameters were determined:

cholesterol	globulin (calculated)
triglycerides	high-density lipoprotein cholesterol
total protein	non-high-density lipoprotein cholesterol (calculated)
albumin	serum corticosterone

M. Humoral Immune Function

On test day 23, animals were injected intravenously in the lateral tail vein with 0.5 mL of 4×10^8 SRBC/mL (Covance, Denver, Pennsylvania, U.S.A.). On test day 29, serum was collected from each rat and frozen (see L.2. Clinical Chemistry).

Humoral immune function was evaluated by examining sera from individual animals for SRBC-specific IgM levels with an enzyme-linked immunosorbent assay (ELISA).[7] The serum from each animal was assayed as 10 serial, 2-fold dilutions, with 1 replicate per dilution. The optical density (OD) of the contents of the reaction well was measured at the 405 nm wavelength with a MR 5000 Microplate Reader (Dynex Technologies). SRBC-specific serum IgM titer data were analyzed with Revelation Software Version 2.0 (Dynex Technologies). For each serum sample, a semi-log graph of the data was created and the linear portion of the curve was identified by using a log-log curve fit. A slope between -0.600 and -1.200 was obtained. The serum dilution expected to produce an OD of 0.5 was determined by regression analysis. The "titer" of each animal was defined as the reciprocal of the serum dilution that had an OD value of 0.5. If no points had an OD value of greater than or equal to 0.5, the reciprocal of the starting dilution closest to an OD value of 0.5 was used as the titer.

Sera previously collected from rats injected with SRBC and dosed for 6 days with 20 mg/kg of the known immunosuppressive agent, cyclophosphamide monohydrate, or vehicle were run concurrently with the study samples to demonstrate that the assay functioned properly. For any test samples that needed to be rerun due to a poor curve fit or slope, pooled male or female cyclophosphamide monohydrate or vehicle serum samples were concurrently run. The pooled samples consisted of equal aliquots of serum taken from either the male or female rats dosed with cyclophosphamide monohydrate or vehicle.

N. Anatomic Pathology Evaluation

After 29 days on study, all rats from each dose group (0, 0.3, 1, 10, 30, and 30/0 mg/kg body weight) were sacrificed and necropsied for evaluation of subchronic toxicity. The order of

sacrifice for scheduled deaths was stratified across groups. Rats were fasted at least 15 hours before their scheduled sacrifice.

All rats survived the duration of the study and were euthanized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed and final body and organ weights were recorded.

The following tissues were collected from all 60 rats (10/sex/group) on study.

Digestive System	Nervous System
liver[a]	brain[a,c] (3 sections)
Hematopoietic System	**Musculoskeletal System**
spleen[a]	femur/knee joint
thymus[a]	sternum
popliteal lymph node	
mesenteric lymph node	Other
bone marrow[b]	gross observations

a Organs were weighed at necropsy.
b Bone marrow was collected with the femur and sternum.
c Including cerebrum, cerebellum, medulla/pons

Organ weight ratios (% final body weight, % brain weight) and group mean values for weighed organs were calculated.

All tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin (H&E), and examined microscopically by a veterinary pathologist. Microscopic findings were graded on a 4-point scale based on the severity or extent of the change (grade 1 = minimal; grade 2 = mild; grade 3 = moderate; grade 4 = severe).

All tissues collected from control (0 mg/kg) and high-dose (30 and 30/0 mg/kg) rats were processed to slides and evaluated microscopically. In addition, the following organs were examined from intermediate-dose rats in order to determine a no-observed-effect level for test substance-related microscopic findings: liver and spleen.

Gross observations (recorded at necropsy) were examined microscopically for all animals.

O. Total Cell Counts

The following procedures were used for preparation of spleen and thymus single-cell suspensions for enumeration of total cell counts from each spleen or thymus:

- The weight of the halved spleen or thymus (tissue) was documented; the half was placed in a labeled 15 mL centrifuge tube containing 5 mL Hank's Balanced Salt Solution (HBSS/H) and put on ice.

- The halved tissue/HBSS/H was poured into a small petri dish and cut into small pieces.
- The tissue/HBSS/H was poured into a Stomacher 80 Lab System® bag and placed into the Stomacher 80 Lab System® on "high" setting for 120 seconds (spleen) or 60 seconds (thymus).
- After the Stomacher 80 Lab System® stopped, the cell suspension was pipetted back into the original centrifuge tube, rinsing the bag with 3 mL HBSS/H and adding that to the centrifuge tube.
- The centrifuge tube was inverted 2 or 3 times and left on ice for approximately 10 minutes to allow debris to settle to the bottom of the tube.
- The supernatant was transferred to a new centrifuge tube and the volume of the supernatant was documented.
- Total cell counts were determined from each tissue by hemacytometer.

P. Electron Microscopy Evaluation

A section of liver from 2 control rats (105 and 106) and 2 rats from the 30 mg/kg group (905 and 906) was placed in cassettes, in a container of formalin, and shipped to Experimental Pathology Laboratories, Inc (EPL®) and evaluated by transmission electron microscopy. As a subcontractor to EPL®, the Laboratory for Advanced Electron and Light Optical Methods, College of Veterinary Medicine, North Carolina State University processed the tissues for electron microscopy and prepared electron photomicrographic images under the direction of Dr. Michael Dykstra. The printed electron photomicrographic images were provided to EPL® for evaluation by an ACVP-certified veterinary pathologist who interpreted the images and prepared a final report of the electron microscopic evaluation.

Q. Statistical Analyses

For all statistical analyses, significance was judged at $p < 0.05$. Comparisons were made of the dosed groups to the control group (Group I). Comparisons were also made between Group IX and Group XI.

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Humoral Immune Function Data[a] Clinical Pathology Organ Weights Total Cell Counts	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] followed by Dunnett's test[11,12,13]	Kruskal-Wallis test[14] followed by Dunn's test[15]

a SRBC-specific serum IgM antibody titer data were transformed to Log_2 to obtain normality or homogenous variances.

b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed by Dunn's test.

RESULTS AND DISCUSSION

Analytical Evaluation

A. Chromatography

(Figures 1-2)

PFOA dissociated from APFO and 1, 2-di-^{13}C PFOA eluted together from the HPLC column with a retention time of approximately 4.5 minutes. The mixture was separated into 2 resolved peaks at 369 m/z and 370 m/z, respectively, by MS/MS detection. Representative LC/MS/MS chromatograms are shown in Figures 2(a - e). Test substance was not detected in the 0 mg/mL samples.

B. Recovery Samples

(Table 1)

Detailed analytical results of recovery samples are summarized in Table 1. The variability of the analytical method was demonstrated by the coefficients of variation of the recovery results at each targeted dosing concentration (approximately 0.03, 0.1, 1, and 3 mg/mL) over the course of the study. The range of the measured concentrations of APFO for the 0.03 mg/mL level was 101.7% to 108.3% of nominal (mean percent recovery = 105.0% ± 5%, C.V. = 5%). The range of the measured concentrations of APFO for the 0.1 mg/mL level was 104.0% to 109.6% of nominal (mean percent recovery = 106.8% ± 4%, C.V. = 4%). The range of the measured concentrations of APFO for the 1 mg/mL level was 102.0% to 105.0% of nominal (mean percent recovery = 103.5 ± 2%, C.V. = 2%). The range of the measured concentrations of APFO for the 3 mg/mL level was 101.7% to 107.0% of nominal (mean percent recovery = 104.4 ± 4%, C.V. = 4%). Based on these data, the analytical method performed satisfactorily for the concentration range of the dosing samples in the study.

C. Concentration Verification, Uniformity of Mixing, and 5-Hour Room Temperature Stability Samples

(Table 2)

Analytical results from dosing solutions prepared on October 17, 2005 analyzed for concentration verification, uniformity of mixing, and 5-hour room temperature stability are shown in Table 2.

The following table summarizes the results for concentration verification, uniformity of mixing, and 5-hour room temperature stability analyses.

Preparation Date	Nominal mg/mL	Measured[a] mg/mL	Average % Nominal	C.V. (%)	Stability[b] % Nominal
17-October-2005	0	ND[c]	---	---	---
	0.03	0.0278, 0.0277	92.7	0.3	96.3
	0.1	0.0966, 0.0979	97.3	0.9	99.0
	1	0.979, 1.04, 1.03[d]	102.0	3	96.9
	3	3.16, 3.06	103.7	2	102.0

a Duplicate samples analyzed.
b Stability samples held for 5 hours at room temperature.
c Denotes not detected.
d Data obtained from one of the duplicate initial analyses and 2 repeats from the re-diluted sample.

The data for samples submitted on October 17, 2005 show that the test substance was at the targeted levels (± 7.3% of nominal), uniformly mixed (CV's = 0.3%, 0.9%, 3%, and 2%, respectively), and stable when held for 5 hours at room temperature in the vehicle. Test substance was not detected in the 0 mg/mL sample.

D. Concentration Verification and Uniformity of Mixing Samples

(Table 3)

Analytical results from dosing solutions prepared on November 15, 2005 analyzed for concentration verification and uniformity of mixing are shown in Table 3.

The following table summarizes the results for concentration verification and uniformity of mixing analyses.

Preparation Date	Nominal mg/mL	Measured[a] mg/mL	Average % Nominal	C.V. (%)
15-November-2005	0	ND[b]	---	---
	0.03	0.0276, 0.0272	91.3	1
	0.1	0.0954, 0.0986	97.0	2
	1	1.02, 1.01	102.0	0.7
	3	3.21, 3.23	107.3	0.4

a Duplicate samples analyzed.
b Denotes not detected.

The data for samples submitted on November 15, 2005 show that the test substance was at the targeted levels (± 8.7% of nominal) and uniformly mixed (CV's = 1%, 2%, 0.7%, and 0.4%, respectively). Test substance was not detected in the 0 mg/mL sample.

E. Analytical Conclusions

Data from the analysis of the samples during the study indicate that the test substance was at the targeted concentrations, mixed uniformly, and stable under the conditions of the study. Test substance was not found in the 0 mg/mL samples.

In-Life Measurements

A. Mean Body Weights and Body Weight Gains

(Tables 4-5, Figure 3, Appendix B)

Test substance related adverse reductions in mean body weights and body weight gains were observed at 10, 30 and 30/0 mg/kg. Mean final body weights were 10, 25, and 21% lower than the control group at 10, 30, and 30/0 mg/kg, respectively, as a result of reduced body weight gains; overall body weight gains during test days 0 to 28 were 26, 63 and 50% lower for the same respective doses. The magnitude and onset of the effects on body weight parameters were dose related in that the effects at 30 mg/kg were evident sooner and were more pronounced. There was no appreciable difference in the magnitude of the reduction between the 30 and 30/0 mg/kg, indicating that the shortened dosing period did not have a significant impact on this endpoint.

At 1 mg/kg, overall body weight gain during test days 0 to 28 was 10% lower, resulting in a 4% reduction in mean final body weight. These slight reductions appear to be test substance related; however, they were not statistically significant nor were they considered to be adverse.

Body weight data for animals dosed at 0.3 mg/kg were generally comparable to control group data.

B. Food Consumption and Food Efficiency

(Tables 6-7, Appendix C)

Test substance related adverse reductions in mean daily food consumption and food efficiency were observed at 10, 30 and 30/0 mg/kg; test substance-related effects on these parameters were also observed at 1 mg/kg but these effects at 1 mg/kg were not considered adverse based on the magnitude of the reductions.

Mean daily food consumption was 4, 17 and 16% lower than controls at 10, 30, and 30/0 mg/kg, respectively, during test days 0 to 28.

The combined test substance-related reductions in mean body weight, weight gain, and food consumption resulted in test substance-related reductions in food efficiency. During test days 0 to 28, mean food efficiency was 23, 57 and 42% lower at 10, 30 and 30/0 mg/kg/day.

The effects on food consumption parameters were similar to and consistent with the effects on body weight parameters in that the magnitude and onset of the effects on food consumption and efficiency were dose related terms of onset, severity, and duration of the effects. Additionally, there was no appreciable difference in the magnitude of the reduction of the overall mean daily food consumption between the 30 and 30/0 mg/kg, indicating that the shortened dosing period did not have a significant impact on this endpoint.

At 1 and 10 mg/kg, mean daily food consumption and food efficiency was 3 and 7% lower than controls, respectively. These slight reductions appear to be test substance related; however, they were not statistically significant nor were they considered to be adverse.

Food consumption and food efficiency data for animals dosed at 0.3 mg/kg were generally comparable to control group data.

C. Clinical Observations and Mortality

(Tables 8-9, Appendices D-E)

There was no test substance-related mortality at any level tested; all animals survived to the scheduled sacrifice on test day 29.

Test substance related clinical observations were observed at 30 and 30/0 mg/kg and included wet and/or stained fur, absent or decreased feces, not eating, high carriage, and lethargy. These signs were reported for up to 3 animals in these groups and thus, the incidence was not overwhelming. However, the nature of the signs combined with the effects on body weight and food consumption discussed previously supported that these observations were test substance-related and adverse. Hair loss was reported in up to 3 animals per group; this unremarkable finding was not considered test substance related since the incidence was not dose-related.

Clinical Pathology Evaluation

A. Hematology

(Table 10, Appendix F)

1. Red Blood Cells

Hemolysis was evident in serum of rats dosed with ≥1 mg/kg (see Clinical Chemistry section).

Hemoglobin and hematocrit were mildly decreased in rats dosed with 10 or 30 mg/kg for 29 days (means were 91-92% of the control group mean, respectively; statistically significant), but there were no effects on red blood cell counts. The discordance between red blood cell count and hematocrit was likely due to decreased mean cell volume in rats dosed with 10 or 30 mg/kg for 29 days (hematocrit is the product of mean cell volume and red blood cell count). Means for mean cell volumes were 97 and 95% of the control group mean; (statistically significant at 30 mg/kg). Mean cell hemoglobin, which generally closely parallels mean cell volume, was also decreased in these 2 dose groups (means were 95 and 94% of the control group mean, respectively; statistically significant).

A few rats dosed with 10 or 30 mg/kg for 29 days had increased reticulocytes, although there were no significant changes in mean reticulocyte counts (means were 109 and 112% of the control group mean). Increased red cell distribution width generally correlated with increased reticulocytes in rats from these groups. Mean red cell distribution widths were 111 and 115%, respectively, of the control group mean. Microscopically, some of the rats in these 2 groups had

increased anisocytosis (variation in red cell size; also observed in rats dosed with 1 mg/kg), macrocytosis (increased numbers of larger cells), polychromasia (increased bluish staining of red blood cells), and hypochromasia (pale staining of red blood cells). These changes were consistent with minimally increased reticulocytes in some animals.

Effects on red cell mass parameters were present (red blood cell count) or more pronounced (hemoglobin, hematocrit) in the 30/0 mg/kg group of rats compared to those dosed with 30 mg/kg for 29 days. On test day 29, mean red blood cell count, hemoglobin, and hematocrit ranged from 86-88% of the respective control group means for these 3 parameters (all statistically significant). Decreased red cell mass parameters on test day 29 could be due to one or more of the following processes: increased red cell destruction, red cell loss, or increased plasma volume. The mechanism for decreased red cell mass parameters was not evident from in-life, clinical pathology, or anatomic pathology data. Therefore, the cause of the decreased red cell mass was not determined.

Reticulocytes were moderately increased in rats dosed with 30/0 mg/kg. Mean reticulocyte count was 197% of the control group mean. Consistent with the increase in reticulocyte counts, red cell distribution width was increased (mean was 123% of the control group mean). Microscopically, this group had increased anisocytosis, macrocytosis, polychromasia, hypochromasia, and acanthocytosis (red blood cells with blunt surface projections). All morphologic changes in red cells occurred at greater incidence or at higher severity grades in these rats compared to rats dosed with APFO for 29 days. These red blood cell changes also correlated with histologic evidence of increased extramedullary hematopoiesis, which was observed in 7 of ten 30/0 mg/kg rats, but in none of the 30 mg/kg rats after 29 days of dosing.

2. White Blood Cells

White blood cell counts were minimally increased, primarily due to increases in lymphocytes, in some rats dosed with 10 or 30 mg/kg for 29 days (variable statistical significance). Means were 130 and 137% (total white blood cell count), and 133 and 140% (lymphocyte count) of respective control group means. Individual rats dosed with 10 or 30 mg/kg with higher total white blood cell and lymphocyte counts generally had higher neutrophil, monocyte, and large unstained cell (LUC) counts as well, resulting in mean neutrophil, monocyte and LUC counts that were 114-147% of the control group means. Due to the normal range and variability of total and individual white blood cell counts, these changes did not result in statistically different means. LUCs are cells that cannot be identified as one of the 5 major leukocyte types by the Advia 120 automated hematology analyzer, and normally comprise a small percentage of the total leukocyte population. The LUC count normally includes mostly lymphocytes and monocytes. Consistent with this observation, in this study, the rats with the highest LUC counts usually had the highest lymphocyte and/or monocyte counts. The changes observed in total and individual white blood cell counts are consistent with inflammation. Histologically, there were no findings observed that correlated with these white blood cell changes.

In rats that were dosed with 30/0 mg/kg, total white cell and lymphocyte counts were generally similar to their respective control group means, with the exception of a few rats with higher total white blood cell and lymphocyte counts (rats 1106 and 1107). Monocyte and large unstained cell counts for rats dosed with 30/0 mg/kg were similar to those of rats dosed for 29 days with 10

or 30 mg/kg in that the counts of most rats were similar to controls, but a few rats had higher monocyte and LUC counts. Therefore, there was no recovery.

Mean eosinophil counts were minimally decreased in rats dosed with ≥0.3 mg/kg for 29 days (not statistically significant). These decreases were the result of high eosinophil counts in 3 control rats. There was no dose response in changes in eosinophil counts despite the 100-fold difference in dose administered in either terminal or recovery animals. In rats that were dosed with 30/0 mg/kg, eosinophil counts were similar to groups dosed with ≥0.3 mg/kg for 29 days. Therefore, the apparent decreases in eosinophil counts after 29 days of dosing at ≥0.3 mg/kg and in 30/0 mg/kg rats is of uncertain relationship to treatment.

B. Clinical Chemistry

(Table 11, Appendix F)

Hemolysis was evident in serum of rats dosed with ≥1 mg/kg. Hemolysis is graded as none, trace, small, moderate or large. In this study, all samples had either none, trace, or small hemolysis. The incidence of serum graded trace to small for hemolysis was 1/10, 0/10, 3/10, 9/10, and 7/10 in rats dosed with 0, 0.3, 1, 10, or 30 mg/kg, respectively. In rats that were dosed with 30/0 mg/kg, trace to small hemolysis was observed in 6/10 rats, and the severity was similar to that observed after 29 days of dosing at 30 mg/kg.

Total cholesterol was decreased in rats dosed with 0.3 or 1 mg/kg for 29 days. Means were 64 and 69% of the control group mean, respectively (statistically significant). Cholesterol concentrations of rats dosed with 10 or 30 mg/kg, although higher than those dosed with lower doses, were still lower than controls (means were 81 and 84% of the control group mean, respectively; not statistically significant). The decreases in cholesterol were due to decreases in both HDL and non-HDL cholesterol. HDL cholesterol was decreased by a similar degree in all groups dosed with the test substance for 29 days; means were 75-79% of the control group mean (variable statistical significance). Non-HDL cholesterol, like total cholesterol, was lower in rats dosed with 0.3 or 1 mg/kg (means were 58 and 63% of control group mean; statistically significant) than in rats dosed with 10 or 30 mg/kg (means were 85 and 88% of control group mean; statistically significant).

In rats that were dosed with 30/0 mg/kg, total, HDL, and non-HDL cholesterol concentrations were similar to controls, suggesting recovery for most rats. However, total, HDL, and non-HDL cholesterol concentrations were mildly higher in one recovery rat (1103), and lower in another recovery rat (1107) compared to other animals in the 30/0 mg/kg group.

Triglyceride was decreased in rats dosed with ≥0.3 mg/kg for 29 days. The dose-response was flat across the doses tested; means were 69, 75, 68, and 66% of control group means for rats dosed with 0.3, 1, 10, or 30 mg/kg, respectively (variable statistical significance). Triglycerides were still decreased in rats that were dosed with 30/0 mg/kg (mean was 69% of the control group mean), indicating a lack of recovery for triglyceride concentrations.

Albumin was increased in a few rats dosed with 1 mg/kg, and in most rats dosed with 10 or 30 mg/kg. Means were 106, 112, and 115% of the control group mean, respectively (variable statistical significance). In rats that were dosed with 30/0 mg/kg, albumin was similar to that of

rats dosed with 30 mg/kg for 29 days (with the exception of one male, rat 1109, with lower albumin). Mean concentration for rats dosed with 30/0 mg/kg was 112% of the control group mean, indicating a lack of recovery for albumin concentration.

Globulin was decreased in rats dosed with 10 or 30 mg/kg. Means were both 89% of the control group mean. In rats dosed with 30/0 mg/kg, globulin was similar to that of controls (with the exception of one male, rat 1109, with low globulin), indicating recovery for globulin concentrations.

Serum corticosterone was increased in a few rats dosed with 10 or 30 mg/kg for 29 days. Concentrations greater than 300 ng/mL (approximate upper bound for corticosterone concentration in non-stressed rats) were observed in 0/10, 0/10, 0/10, 2/10, and 4/10 rats dosed with 0, 0.3, 1, 10, or 30 mg/kg, respectively. The higher corticosterone concentrations in some rats dosed with 10 or 30 mg/kg resulted in mean concentrations that were 135 and 196% of controls, respectively. These changes are indicative of physiological stress. In rats that were dosed with 30/0 mg/kg, serum corticosterone concentrations were generally similar to controls, indicating recovery.

C. Clinical Pathology Conclusions

Rats dosed with ≥0.3 mg/kg had decreased serum total, HDL, and non-HDL cholesterol, and decreased triglycerides. Rats dosed with ≥1 mg/kg had increased microscopic red cell morphologic changes and hemolyzed serum. Rats dosed with ≥10 mg/kg had decreased hemoglobin, hematocrit, mean cell volumes, and mean cell hemoglobin concentrations; increased reticulocyte counts and red cell distribution width, increased total white blood cell, neutrophil, monocyte, and LUC counts; increased serum albumin and decreased serum globulin concentrations, and increased serum corticosterone concentrations. Rats in the 30/0 mg/kg group had more pronounced red cell mass effects and red cell morphologic changes compared to those dosed with 30 mg/kg for 29 days. Parameters with complete recovery in rats dosed with 30/0 mg/kg were serum total, HDL, and non-HDL cholesterol, globulin, and corticosterone concentrations.

Immunotoxicity

A. Humoral Immune Function

(Tables 12-13, Appendices G-H)

No test substance-related evidence of immunosuppression was observed in male rats at any concentration tested; the IgM titers were generally comparable across all groups.

For the individual and pooled positive control sera, the primary humoral immune response to SRBC was decreased by 57 and 55%, respectively. Therefore, the SRBC-specific ELISA test system was valid for this study.

Anatomic Pathology Evaluation

A. Cause of Death

There were no test substance-related deaths. All 60 rats on study survived until the scheduled sacrifice on test day 29.

B. Final Body and Organ Weight Data

(Table 14, Appendix I)

Following 28-days of daily gavage administration of the test substance, there was a test substance-related decrease in final body weights and increase in liver weights. Mean final body weights were decreased at dose levels ≥10 mg/kg of the test substance. Mean liver weight parameters were increased at dose levels ≥0.3 mg/kg.

Text Table 1: Mean Absolute and Relative (% body weight) Organ Weights in Male Rats

Group:	I	III	V	VII	IX	XI
Dose (mg/kg):	0	0.3	1	10	30	30/0
Number of Rats/Sex:	10	10	10	10	10	10
Final Body Wt. (g)	423.1	419.7	410.0	377.0*	314.4*	333.8*
Liver	(10)	(10)	(10)	(10)	(10)	(10)
absolute wt. (g)	13.179	14.379	17.227*	21.469*	18.684*	16.206*^
% body wt.	3.113	3.419	4.194	5.680**	5.931**	4.849**
Spleen	(10)	(10)	(10)	(10)	(10)	(10)
absolute wt. (g)	0.844	0.872	0.835	0.808	0.674	0.780
% body wt.	0.199	0.208	0.203	0.215	0.215	0.232
Thymus	(10)	(10)	(10)	(10)	(10)	(10)
absolute wt. (g)	0.568	0.604	0.559	0.581	0.487	0.639^
% body wt.	0.133	0.144	0.136	0.153	0.153	0.191*^

wt. = weight; ( ) = number in parenthesis is the number of organs weighed.
Underlined values were interpreted to be test-substance related effects, as compared to control values.
* = statistically significant (Dunnett/Tamhane-Dunnett parametric pairwise test), compared to control value.
** = statistically significant (Dunn's non-parametric pairwise test), compared to control value.
^ = statistically significant (Dunn's non-parametric pairwise test) change in Group XI value compared to Group IX value.

1. Final Body Weight

Mean final body weights were decreased 11%, 26%, and 21% in the 10, 30, and 30/0 mg/kg dose groups, respectively, as compared to the control value. All decreases were statistically significant. Mean final body weights in the 0.3 and 1 mg/kg dose groups were similar to the control values.

There was a small, statistically insignificant increase in the mean final body weight of the 30/0 mg/kg dose group, as compared to the 30 mg/kg dose group. This increase suggests partial recovery from the test substance-related final body weight decrease in the 6 recovery days following the injection of sheep red blood cells.

2. Liver

Mean absolute liver weights were increased 9%, 31%, 63%, 42%, and 23% in the 0.3, 1, 10, 30, and 30/0 mg/kg dose groups, respectively, as compared to the control value. Mean relative (% body weight) liver weights were similarly increased (10%, 35%, 82%, 91%, and 56%, respectively). All increases were statistically significant, except for those in the 0.3 mg/kg dose group and the mean relative liver weight in the 1 mg/kg dose group.

The increased liver weights, at all dose levels, correlated with the microscopic finding of minimal to moderate hepatocellular hypertrophy. It also correlated with the gross observation of liver discoloration in a few rats at doses ≥10 mg/kg.

3. Other

All other individual and mean organ weight differences were considered to be spurious or secondary to the decrease in final body weights. Mean relative brain weights (% body weight) were increased only at doses (≥10 mg/kg) that produced significantly decreased body weights. Similarly, small, statistically insignificant, decreases in mean absolute, and increases in mean relative (% body weight), spleen and thymus weights were interpreted to be secondary to changes in final body weights. The lack of any gross or microscopic effects in the brain, spleen, and thymus further suggests that these organ weight differences were a function of body weight and not organ-specific effects.

C. Gross Observations

(Table 15, Appendix J)

At the terminal sacrifice, test substance-relate gross observations were limited to discoloration of the liver in a few rats at doses ≥10 mg/kg.

Text Table 2: Incidences of Test Substance-Related Gross Observations in Male Rats

Group:	I	III	V	VII	IX	XI
Dose (mg/kg):	0	0.3	1	10	30	30/0*
Number of Rats/Group:	10	10	10	10	10	10
Liver						
Discoloration	0	0	0	1	2	1

Underlined values were interpreted to be test-substance related increases, as compared to control values.
* Not dosed with test substance following immunology challenge.

The gross liver discoloration observed in the 4 rats given ≥10 mg/kg of the test compound was considered to be a result of the microscopic finding of hepatocellular hypertrophy.

D. Microscopic Findings

(Table 16, Appendix J)

Microscopic examination of the liver demonstrated minimal to mild hepatocellular hypertrophy at 0.3 and 1 mg/kg and moderate hepatocellular hypertrophy at ≥10 mg/kg.

Microscopic examination of lymphohematopoietic organs (spleen, thymus, bone marrow, lymph nodes) revealed increased hematopoiesis in the spleen of high-dose recovery rats (30/0 mg/kg).

The thymus, mesenteric lymph nodes and popliteal lymph nodes had no test substance-related effects.

Text Table 3: Incidences of Test Substance-Related Microscopic Findings in Male Rats

Group:	I	III	V	VII	IX	XI
Dose (mg/kg):	0	0.3	1	10	30	30/0*
Number of Rats/Group:	10	10	10	10	10	10
Liver	(10)	(10)	(10)	(10)	(10)	(10)
Hypertrophy, hepatocellular	0	5 [1.0]	10 [1.7]	10 [3.0]	10 [3.0]	10 [3.0]
Necrosis, focal	0	0	0	1 [1.0]	4 [1.0]	1 [1.0]
Spleen	(10)	(10)	(10)	(10)	(10)	(10)
EMH, increased	0	0	1 [1.0]	0	0	7 [1.3]

[ ] = Number in brackets is the average grade (grades 1 – 4) when lesion is present (i.e., sum of grades ÷ # animals with lesion). Grading scale: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe.
( ) = number in parenthesis is the number of organs examined; EMH = Extramedullary hematopoiesis.
Underlined values were interpreted to be test-substance related increases, as compared to control values.
* Not dosed with test substance following immunology challenge.

1. Liver

a. Hepatocellular hypertrophy

Panlobular hepatocellular hypertrophy was observed in all but 5 of the rats given the test substance and the incidence and severity were dose related. Hypertrophy was present in 0/10, 5/10, 10/10, 10/10, 10/10, and 10/10 rats given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. The hypertrophy was graded as minimal in the 5 affected rats given 0.3 mg/kg, minimal in 3/10 and mild in 7/10 rats given 1 mg/kg, and moderate in all rats given ≥10 mg/kg.

The hepatocellular hypertrophy was characterized by an increase in the size of all hepatocytes due to an increase in cytoplasmic volume. The cytoplasm had a uniformly eosinophilic granular appearance consistent with peroxisome proliferation.

Hepatocellular hypertrophy correlated with increased mean liver weight parameters at all doses. Although the 30/0 mg/kg group still had moderate hypertrophy (grade 3 of 4), the decrease in mean liver weights, relative to the 30 mg/kg group suggests that there was some hepatocellular shrinkage and/or loss that was microscopically unapparent.

b. Focal necrosis

Focal necrosis was also observed in several rats given ≥10 mg/kg of the test substance. The incidence was mildly dose related. Focal necrosis was present in 0/10, 0/10, 0/10, 1/10, 4/10, and 1/10 rats given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. All were graded minimal. A decrease in the incidence was apparent in the 30/0 mg/kg group, as compared to the 30 mg/kg group.

Focal necrosis was characterized by the focal or multifocal coagulative necrosis of a cluster of hepatocytes. The distribution was usually subcapsular and the pattern was non-zonal. Focal coagulative necrosis of hepatocytes clusters is a common secondary effect of hepatocellular hypertrophy and is most likely the result of secondary focal ischemia.

2. Spleen

a. Increased extramedullary hematopoiesis

An increase in the incidence of splenic extramedullary hematopoiesis (EMH) was considered test substance related only in high-dose rats allowed a recovery period (30/0 mg/kg). Minimal to mild increased EMH was observed in 0/10, 0/10, 1/10, 0/10, 0/10, and 7/10 rats given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively.

The increased splenic EMH in the high-dose recovery rats was erythrocytic and correlated with the hematology findings, which included decreased red cell mass parameters and increased circulating reticulocytes (see Clinical Pathology).

3. Other

All other microscopic observations in this study were consistent with normal background lesions in rats of this age and strain.

E. Anatomic Pathology Conclusions

There were no test substance-related deaths. All 60 rats on study survived until the scheduled sacrifice on test day 29.

Following 28-days of daily gavage administration of the test substance, there was a test substance-related decrease in final body weights and increase in liver weights. Mean final body weights were decreased at dose levels ≥10 mg/kg of the test substance. Mean liver weight parameters were increased at dose levels ≥0.3 mg/kg.

At the terminal sacrifice, test substance-related gross observations were limited to discoloration of the liver in a few rats at doses ≥10 mg/kg.

Microscopic examination of the liver demonstrated minimal to mild hepatocellular hypertrophy at 0.3 and 1 mg/kg and moderate hepatocellular hypertrophy at ≥10 mg/kg.

Microscopic examination of lymphohematopoietic organs (spleen, thymus, bone marrow, lymph nodes) revealed increased hematopoiesis in the spleen of rats dosed with 30/0 mg/kg.

The thymus, mesenteric lymph nodes and popliteal lymph nodes had no test substance-related effects.

Total Cell Counts

A. Spleen Cell Number

(Table 17, Appendix K)

No significant changes in total spleen cell number compared to control rats were noted in any animal treated with any dose of APFO. A 10% increase was observed at 10 mg/kg and a 16% decrease was observed at 30 mg/kg, but neither value was statistically different than vehicle control.

B. Thymus Cell Number

(Table 17, Appendix K)

No significant changes in total thymocyte number compared to control rats were noted in any animals treated with any dose of APFO. For rats in the 30/0 mg/kg group, an increase in thymocyte number was observed, which was statistically greater than rats who continued to receive 30 mg/kg APFO, but not greater when compared to vehicle control.

CONCLUSIONS

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for APFO for systemic toxicity in male rats was less than 0.3 mg/kg, whereas the NOAEL for immunotoxicity was 30 mg/kg.

RECORDS AND SAMPLE STORAGE

Specimens (if applicable), raw data, the protocol, amendments (if any), and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

Laboratory-specific raw data such as personnel files, instrument, equipment, refrigerator and/or freezer raw data will be retained at the facility where the work was done.

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TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular (cell) volume
MCH - mean corpuscular (cell) hemoglobin
MCHC - mean corpuscular (cell) hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell

Summary of Clinical Chemistry Values

CHOL - cholesterol
TRIG - triglycerides
TP - total protein
ALB - albumin
GLOB - globulin
HDL - high-density lipoprotein cholesterol
NHDL - non-high-density lipoprotein cholesterol
SCORT - serum corticosterone

NOTES:

Summary of Hematology Values
Summary of Clinical Chemistry Values
Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

TABLES

EXPLANATORY NOTES (Continued)

NOTES: (Continued)

Summary of Total Cell Counts

$$\text{Organ Weight as Percent of Body Weight} = \frac{\text{Organ Weight (g)}}{\text{Final Body Weight (g)}} \times 100$$

$$\text{Total Number of Organ Cells } (\times 10^8) = \frac{\text{Organ Weight (g)}}{\text{Half Organ Weight (g)}} \times \text{Organ Cell Suspension Volume (mL)} \times \text{Number of Cells in Half Organ } (\times 10^6 \text{ cells/mL}) \div 100$$

Table 1
Recovery of APFO Added to Dosing Vehicle

Sample Type	APFO (mg/mL)		Percent
	Nominal	Measured	Nominal
RECOVERY[A]	0.0302	0.0327	108.3
RECOVERY[B]	0.0300	0.0305	101.7
		Mean	***105.0 ± 5, C.V. 5%***
RECOVERY[A]	0.104	0.114	109.6
RECOVERY[B]	0.100	0.104	104.0
		Mean	***106.8 ± 4, C.V. 4%***
RECOVERY[A]	1.00	1.02	102.0
RECOVERY[B]	1.00	1.05	105.0
		Mean	***103.5 ± 2, C.V. 2%***
RECOVERY[A]	3.00	3.05	101.7
RECOVERY[B]	3.00	3.21	107.0
		Mean	***104.4 ± 4, C.V. 4%***

[A] Processed with dosing samples submitted October 17, 2005 for concentration verification, uniformity of mixing, and 5-hour room temperature stability analyses.

[B] Processed with dosing samples submitted November 15, 2005 for concentration verification and uniformity of mixing analyses.

Table 2
Concentration Verification, Uniformity of Mixing, and 5-Hour Room Temperature Stability of APFO in Dosing Solutions

Sample Date Sample Type[A]	APFO (mg/mL) Nominal	 Measured	Percent Nominal
15-November-2005			
Concentration Verification			
Control	0	ND[B]	----
#1	0.03	0.0278	92.7
#2	0.03	0.0277	92.3
	Mean:	***0.0278 ± 0.0001***	***(92.7)***
		C.V. 0.3%	
#1	0.1	0.0966	96.6
#2	0.1	0.0979	97.9
	Mean:	***0.0973 ± 0.0009***	***(97.3)***
		C.V. 0.9%	
#1	1	0.979	97.9
#1[C]	1	1.04	104.0
#2[C]	1	1.03	103.0
	Mean:	***1.02 ± 0.03***	***(102.0)***
		C.V. 3%	
#1	3	3.16	105.3
#2	3	3.06	102.0
	Mean:	***3.11 ± 0.07***	***(103.7)***
		C.V. 2%	
Stability[D]			
	0.03	0.0289	96.3
	0.1	0.0990	99.0
	1	0.969	96.9
	3	3.06	102.0

(A) Duplicate analyses per level performed for concentration verification. Mean, S.D. and C.V. calculated to verify uniformity of mixing.
(B) Denotes not detected.
(C) Duplicate analyses from the re-diluted sample.
(D) Samples held at room temperature for 5 hours.

Table 3
Concentration Verification and Uniformity of Mixing of APFO in Dosing Solutions

Sample Type[A] Sample Date	APFO (mg/mL) Nominal		Measured	Percent Nominal
Concentration Verification 11-October-2005 Control	0		ND[B]	----
#1	0.03		0.0276	92.0
#2	0.03		0.0272	90.7
		Mean:	***0.0274 ± 0.0003***	***(91.3)***
			C.V. 1%	
#1	0.1		0.0954	95.4
#2	0.1		0.0986	98.6
		Mean:	***0.0970 ± 0.002***	***(97.0)***
			C.V. 2%	
#1	1		1.02	102.0
#2	1		1.01	101.0
		Mean:	***1.02 ± 0.008***	***(102.0)***
			C.V. 0.7%	
#1	3		3.21	107.0
#2	3		3.23	107.7
		Mean:	***3.22 ± 0.01***	***(107.3)***
			C.V. 0.4%	

(A) Duplicate analyses per level performed for concentration verification. Mean, S.D. and C.V. calculated to verify uniformity of mixing.
(B) Denotes not detected.

Table 4
Mean Body Weights of Male Rats

DAYS ON TEST	MEAN BODY WEIGHTS (g)					
	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
0	269.1 11.6(10)	270.3 11.3(10)	270.6 13.7(10)	270.5 14.1(10)	271.3 8.9(10)	268.4 8.7(10)
7	329.8 15.8(10)	328.5 15.2(10)	328.2 18.4(10)	314.7 17.9(10)	278.0@ 37.4(10)	275.0@ 47.0(10)
14	378.8 20.1(10)	375.0 20.5(10)	373.7 25.5(10)	358.0 21.2(10)	310.7@ 28.3(10)	298.5@ 49.9(10)
21	424.0 24.4(10)	419.7 24.4(10)	412.6 34.5(10)	387.5 30.1(10)	322.0* 38.0(10)	322.2* 45.4(10)
28	453.4 26.5(10)	446.6 30.7(10)	437.2 38.7(10)	407.5* 34.8(10)	339.6* 36.1(10)	359.8* 39.8(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; no significant differences between IX and XI were detected.

Table 5
Mean Body Weight Gains of Male Rats

DAYS ON TEST	MEAN BODY WEIGHT GAINS (g)					
	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
0-7	60.7 7.8(10)	58.2 9.4(10)	57.6 8.7(10)	44.2 10.2(10)	6.7@ 35.4(10)	6.6@ 45.0(10)
7-14	49.0 8.5(10)	46.5 7.2(10)	45.5 7.5(10)	43.3 10.0(10)	32.7 19.5(10)	23.5* 16.9(10)
14-21	45.3 8.6(10)	44.7 6.6(10)	38.9 10.7(10)	29.5* 9.5(10)	11.3* 13.6(10)	23.7*† 11.9(10)
21-28	29.3 3.9(10)	26.9 7.4(10)	24.7 9.5(10)	20.0 7.7(10)	17.6@ 8.8(10)	37.5† 19.0(10)
OVERALL 0-28	184.3 21.2(10)	176.3 25.7(10)	166.6 28.6(10)	137.1* 30.9(10)	68.3* 34.3(10)	91.4* 38.3(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 6
Mean Daily Food Consumption by Male Rats

DAYS ON TEST	MEAN DAILY FOOD CONSUMED PER ANIMAL (g)					
	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
7	28.8 1.8(10)	28.0 2.1(10)	28.5 2.2(10)	26.4 1.6(10)	20.1@ 6.7(10)	20.9@ 6.6(10)
14	29.2 2.3(10)	28.7 2.6(10)	28.7 2.7(10)	29.1 2.0(10)	27.9 3.6(10)	25.3* 4.8(10)
21	30.0 2.1(10)	29.2 2.6(10)	28.5 3.0(10)	29.2 2.7(10)	24.0* 5.2(10)	25.5* 2.7(10)
28	30.2 1.7(10)	29.7 2.7(10)	28.5 2.7(10)	29.1 2.4(10)	26.5* 2.0(10)	27.0* 2.7(10)
OVERALL 0-28	29.5 1.8(10)	28.9 2.4(10)	28.6 2.5(10)	28.4 2.0(10)	24.6* 3.2(10)	24.7* 2.9(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; no significant differences between IX and XI were detected.

Table 7
Mean Daily Food Efficiency of Male Rats

	MEAN DAILY FOOD EFFICIENCY (g weight gain/g food consumed)					
DAYS ON TEST	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
0-7	0.301 0.029(10)	0.296 0.035(10)	0.287 0.029(10)	0.238 0.047(10)	-0.070@ 0.401(10)	-0.209@ 1.003(10)
14	0.240 0.033(10)	0.231 0.024(10)	0.226 0.025(10)	0.211 0.039(10)	0.164 0.096(10)	0.127* 0.081(10)
21	0.215 0.033(10)	0.218 0.022(10)	0.192 0.037(10)	0.143* 0.038(10)	0.054* 0.080(10)	0.135* 0.078(10)
28	0.139 0.018(10)	0.128 0.027(10)	0.122 0.038(10)	0.096@ 0.032(10)	0.096@ 0.049(10)	0.193† 0.076(10)
OVERALL 0-28	0.222 0.018(10)	0.217 0.019(10)	0.207 0.019(10)	0.171* 0.029(10)	0.096* 0.042(10)	0.129*† 0.044(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 8
Summary of Daily Animal Health Observations in Male Rats

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group IX 30/0 mg/kg (Recovery)
ANIMAL COUNT:	10	10	10	10	10	10
Wet Fur	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Feces Absent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (10%)
Decreased Feces	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)	1 (10%)
Not Eating	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (30%)	2 (20%)
Stain Fur/Skin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)

Data arranged as: number of animals (percent of group) for which an observation was recorded

Table 9
Summary of Detailed Clinical Observations in Male Rats

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group IX 30/0 mg/kg (Recovery)
ANIMAL COUNT:	10	10	10	10	10	10
Wet Fur	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Carriage, High	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Feces Absent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Hair Loss	1 (10%)	0 (0%)	1 (10%)	1 (10%)	3 (30%)	0 (0%)
Lethargic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Not Eating	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)
Stain Fur/Skin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)

Data arranged as: number of animals (percent of group) for which an observation was recorded

Table 10
Summary of Hematology Values for Male Rats

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
RBC ($x10^6/\mu L$)						
DAY 29	7.66 0.20(9)	7.61 0.33(10)	7.60 0.32(10)	7.28 0.50(10)	7.47 0.60(10)	6.75*# 0.34(10)
HGB (g/dL)						
DAY 29	14.9 0.3(9)	14.7 0.5(10)	14.7 0.6(10)	13.5@ 0.7(10)	13.6@ 0.7(10)	12.8@# 0.3(10)
HCT (%)						
DAY 29	46.2 1.0(9)	45.4 1.5(10)	45.6 1.8(10)	42.6* 2.3(10)	42.7* 2.0(10)	40.2*# 1.2(10)
MCV (fL)						
DAY 29	60.3 2.0(9)	59.7 2.0(10)	60.1 2.2(10)	58.5 2.3(10)	57.3* 2.4(10)	59.6 2.8(10)
MCH (pg)						
DAY 29	19.5 0.5(9)	19.3 0.6(10)	19.4 0.7(10)	18.6* 0.8(10)	18.3* 0.7(10)	19.0 0.9(10)
MCHC (g/dL)						
DAY 29	32.3 0.5(9)	32.4 0.3(10)	32.2 0.4(10)	31.8 0.5(10)	31.9 0.5(10)	31.8 0.6(10)

Table 10
Summary of Hematology Values for Male Rats (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
RDW (%)						
DAY 29	11.5	11.4	11.7	12.8@	13.2@	14.2@
	0.3(9)	0.5(10)	0.3(10)	0.7(10)	0.8(10)	2.1(10)
ARET ($x10^3/\mu L$)						
DAY 29	187.3	170.5	177.5	204.5	208.9	369.8@#
	16.5(9)	19.7(10)	24.1(10)	46.2(10)	40.8(10)	88.6(10)
PLT ($x10^3/\mu L$)						
DAY 29	1090	1058	1094	1044	1196	1207
	125(6)	76(10)	111(6)	344(7)	174(7)	162(8)
WBC ($x10^3/\mu L$)						
DAY 29	12.49	11.41	13.28	16.26	17.07*	13.91
	3.48(9)	2.83(10)	2.83(10)	2.69(10)	2.93(10)	4.42(10)
ANEU ($x10^3/\mu L$)						
DAY 29	1.46	1.38	1.55	1.66	1.79	1.46
	0.58(9)	0.49(10)	0.71(10)	0.53(10)	0.59(10)	0.43(10)
ALYM ($x10^3/\mu L$)						
DAY 29	10.40	9.56	11.19	13.87*	14.53*	11.81
	2.80(9)	2.54(10)	2.47(10)	2.41(10)	2.67(10)	4.07(10)

Table 10
Summary of Hematology Values for Male Rats (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
AMON (x10³/µL)						
DAY 29	0.25	0.22	0.26	0.33	0.35	0.29
	0.09(9)	0.09(10)	0.12(10)	0.17(10)	0.15(10)	0.11(10)
AEOS (x10³/µL)						
DAY 29	0.17	0.08	0.09	0.13	0.11	0.10
	0.11(9)	0.04(10)	0.04(10)	0.07(10)	0.07(10)	0.06(10)
ABAS (x10³/µL)						
DAY 29	0.05	0.05	0.07	0.07	0.07	0.06
	0.02(9)	0.03(10)	0.04(10)	0.04(10)	0.04(10)	0.05(10)
ALUC (x10³/µL)						
DAY 29	0.15	0.11	0.13	0.20	0.22	0.19
	0.08(9)	0.03(10)	0.04(10)	0.11(10)	0.12(10)	0.17(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
\# Statistically significant difference from Group IX at $p < 0.05$ by t-test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 11
Summary of Clinical Chemistry Values for Male Rats

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
CHOL (mg/dL)						
DAY 29	64 17(10)	41@ 10(10)	44@ 8(10)	52 10(10)	54 9(10)	73† 23(10)
TRIG (mg/dL)						
DAY 29	68 19(10)	47@ 17(10)	51 20(10)	46@ 15(10)	45@ 11(10)	47@ 16(10)
TP (g/dL)						
DAY 29	6.1 0.2(10)	6.1 0.2(10)	6.2 0.3(10)	6.1 0.4(10)	6.2 0.3(10)	6.5 0.5(10)
ALB (g/dL)						
DAY 29	3.3 0.1(10)	3.4 0.1(10)	3.5 0.2(10)	3.7@ 0.2(10)	3.8@ 0.1(10)	3.7@ 0.3(10)
GLOB (g/dL)						
DAY 29	2.8 0.1(10)	2.8 0.2(10)	2.7 0.2(10)	2.5* 0.2(10)	2.5* 0.3(10)	2.7# 0.2(10)
HDL (mg/dL)						
DAY 29	24 4(10)	18* 3(10)	19* 3(10)	18* 3(10)	19 4(10)	25# 5(10)

Table 11
Summary of Clinical Chemistry Values for Male Rats (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
NHDL (mg/dL)						
DAY 29	40	23@	25@	34	35	47†
	14(10)	8(10)	6(10)	7(10)	5(10)	18(10)
SCORT (ng/mL)						
DAY 29	137	167	147	185	268	131
	95(10)	73(10)	69(10)	91(10)	217(10)	90(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.
\# Statistically significant difference from Group IX at $p < 0.05$ by t-test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 12
Summary of Primary Humoral Immune Response to SRBC for Male Rats Dosed with APFO

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
LOG_2[a]	10.060 1.503(10)	10.368 0.466(10)	9.858 1.503(10)	9.917 1.928(10)	9.906 1.142(10)	9.519 1.198(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Mean $\log_2$ of the serum IgM titer data.

There were no statistically significant differences from control at $p < 0.05$.

Table 13
Summary of Primary Humoral Immune Response to SRBC for Male Rats Dosed With Positive Control

	Saline[a]	Cyclophosphamide 20 mg/kg[a]	Cyclophosphamide 20 mg/kg[b]
LOG_2	9.456 1.147(10)	4.098 0.978(10)	4.241 0.872(2)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Mean $\log_2$ of the SRBC-specific serum IgM titer data for individual samples.
b Log_2 of the SRBC-specific serum IgM titer data for pooled samples.

Table 14
Mean Final Body and Organ Weights from Male Rats

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)						
LIVER	13.179 1.397(10)	14.379 1.604(10)	17.227* 2.860(10)	21.469* 2.864(10)	18.684* 2.866(10)	16.206*† 2.170(10)
SPLEEN	0.844 0.167(10)	0.872 0.209(10)	0.835 0.144(10)	0.808 0.126(10)	0.674 0.085(10)	0.780 0.182(10)
THYMUS	0.568 0.126(10)	0.604 0.123(10)	0.559 0.121(10)	0.581 0.134(10)	0.487 0.171(10)	0.639† 0.110(10)
BRAIN	2.012 0.088(10)	2.111 0.117(10)	2.086 0.087(10)	1.999 0.123(10)	1.992 0.108(10)	1.913 0.129(10)
FINAL BODY WEIGHT (grams)	423.1 26.0(10)	419.7 25.0(10)	410.0 35.2(10)	377.0* 32.8(10)	314.4* 35.1(10)	333.8* 36.1(10)

Table 14
Mean Final Body and Organ Weights from Male Rats (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)						
LIVER/ FINAL BODY * 100	3.113 0.229(10)	3.419 0.250(10)	4.194 0.524(10)	5.680@ 0.385(10)	5.931@ 0.503(10)	4.849@ 0.345(10)
SPLEEN/ FINAL BODY * 100	0.199 0.033(10)	0.208 0.047(10)	0.203 0.021(10)	0.215 0.030(10)	0.215 0.020(10)	0.232 0.039(10)
THYMUS/ FINAL BODY * 100	0.133 0.024(10)	0.144 0.028(10)	0.136 0.024(10)	0.153 0.029(10)	0.153 0.046(10)	0.191*† 0.019(10)
BRAIN/ FINAL BODY * 100	0.477 0.028(10)	0.504 0.030(10)	0.511 0.038(10)	0.533* 0.044(10)	0.639* 0.059(10)	0.577*† 0.052(10)

Table 14
Mean Final Body and Organ Weights from Male Rats (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)						
LIVER/ BRAIN * 100	654.981 61.796(10)	681.399 71.841(10)	825.207* 128.554(10)	1073.082* 119.548(10)	937.602* 129.373(10)	846.704* 95.980(10)
SPLEEN/ BRAIN * 100	41.814 7.212(10)	41.120 8.849(10)	39.940 6.035(10)	40.554 6.671(10)	33.805 3.600(10)	40.732† 8.641(10)
THYMUS/ BRAIN * 100	28.191 5.790(10)	28.563 5.440(10)	26.750 5.543(10)	29.072 6.473(10)	24.424 8.255(10)	33.319† 4.511(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 15
Incidence of Gross Observations in Male Rats

LESIONS	LESION INCIDENCE (Numeric)						
TREATMENT per day	0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg XI Recovery
LIVER	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	9	8	9
LARGE					1	
DISCOLORATION				1	2	1
SPLEEN	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
THYMUS	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
POPLITEAL LYMPH NODE	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
MESENTERIC LYMPH NODE	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10
BRAIN	(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	10	10	10	10

Figures in parentheses are the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

Table 15
Incidence of Gross Observations in Male Rats (Continued)

LESIONS	TREATMENT per day	LESION INCIDENCE (Numeric) 0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg XI Recovery
FEMUR/KNEE JOINT		(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10	10
STERNUM		(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10	10	10

Figures in parentheses are the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

Table 16
Incidences and Lesion Grades of Microscopic Observations in Male Rats

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC) 0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg XI Recovery
LIVER		(10)	(10)	(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		1					
NECROSIS, FOCAL.							
minimal					1	4	1
Total observations per lesion					1	4	1
MINERALIZATION, BILE DUCT.							
minimal					1		
moderate							1
Total observations per lesion					1		1
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal		9	9	9	9	9	8
mild				1	1	1	2
Total observations per lesion		9	9	10	10	10	10
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR.							
minimal			5	3			
mild				7			
moderate					10	10	10
Total observations per lesion			5	10	10	10	10
HYPERPLASIA, BILE DUCT, FOCAL.							
minimal					1		
Total observations per lesion					1		

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

Table 16
Incidences and Lesion Grades of Microscopic Observations in Male Rats (Continued)

LESIONS	LESION INCIDENCE (NUMERIC)					
TREATMENT per day	0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg XI Recovery
LIVER	(10)	(10)	(10)	(10)	(10)	(10)
HEMATOPOIESIS, EXTRAMEDULLARY.						
minimal						1
Total observations per lesion						1
FIBROSIS, FOCAL.						
minimal						1
Total observations per lesion						1
FATTY CHANGE, MEDIAN CLEFT.						
minimal	2					
Total observations per lesion	2					
SPLEEN	(10)	(10)	(10)	(9)	(10)	(10)
NO ABNORMALITY DETECTED	10	10	9	9	10	3
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED.						
minimal			1			5
mild						2
Total observations per lesion			1			7
THYMUS	(10)				(10)	(10)
NO ABNORMALITY DETECTED	10				10	10

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

Table 16
Incidences and Lesion Grades of Microscopic Observations in Male Rats (Continued)

LESIONS	LESION INCIDENCE (NUMERIC)					
	TREATMENT per day	0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg XI Recovery
POPLITEAL LYMPH NODE	(10)				(10)	(10)
NO ABNORMALITY DETECTED	2				7	8
NOT PRESENT IN TISSUE SECTION.	8				3	2
MESENTERIC LYMPH NODE	(10)				(10)	(10)
NO ABNORMALITY DETECTED	10				9	10
DEPLETION/ATROPHY, LYMPHOID.						
minimal					1	
Total observations per lesion					1	
BONE MARROW	(10)				(10)	(10)
NO ABNORMALITY DETECTED	9				10	9
FIBROSIS, FOCAL.						
minimal	1					1
Total observations per lesion	1					1
BRAIN	(10)				(10)	(10)
NO ABNORMALITY DETECTED	9				10	10
PIGMENT, FOCAL.						
minimal	1					
Total observations per lesion	1					

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

Table 16
Incidences and Lesion Grades of Microscopic Observations in Male Rats (Continued)

LESIONS	LESION INCIDENCE (NUMERIC)					
TREATMENT per day	0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg XI Recovery
FEMUR/KNEE JOINT	(10)				(10)	(10)
NO ABNORMALITY DETECTED	10				10	10
STERNUM	(10)				(10)	(10)
NO ABNORMALITY DETECTED	10				10	10

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

Table 17
Summary of Total Cell Counts

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
Final Body Weight (g)	423.12 26.05(10)	419.74 24.95(10)	410.03 35.20(10)	376.95 32.76(10)	314.42 35.14(10)	333.79 36.15(10)
SPLEEN						
Absolute Weight (g)	0.844 0.167(10)	0.872 0.209(10)	0.835 0.144(10)	0.808 0.126(10)	0.674 0.085(10)	0.780 0.182(10)
Weight Ratio (% Body Weight)	0.1988 0.0330(10)	0.2078 0.0469(10)	0.2026 0.0210(10)	0.2146 0.0296(10)	0.2147 0.0198(10)	0.2323 0.0390(10)
Half Weight (g)	0.435 0.089(10)	0.443 0.110(10)	0.421 0.081(10)	0.416 0.062(10)	0.348 0.038(10)	0.401 0.095(10)
Cell Suspension Volume (mL)	6.9 0.5(10)	7.1 0.3(10)	7.4 0.9(10)	7.1 0.5(10)	7.5 1.4(10)	6.8 0.3(10)
Number of Cells in Half (x 10^6 cells/mL)	41.58 17.41(10)	44.22 16.99(10)	43.89 24.34(10)	45.43 16.31(10)	34.32 17.07(10)	44.44 16.55(10)
Total Number of Cells (x 10^8)	5.65 2.60(10)	6.23 2.65(10)	6.45 3.29(10)	6.24 2.10(10)	4.72 1.97(10)	5.79 2.05(10)

Table 17
Summary of Total Cell Counts (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
THYMUS						
Absolute Weight (g)	0.568 0.126(10)	0.604 0.123(10)	0.559 0.121(10)	0.581 0.134(10)	0.487 0.171(10)	0.639 0.110(10)
Weight Ratio (% Body Weight)	0.1335 0.0238(10)	0.1439 0.0281(10)	0.1357 0.0238(10)	0.1531 0.0290(10)	0.1529 0.0463(10)	0.1909 0.0190(10)
Half Weight (g)	0.284 0.069(10)	0.292 0.063(10)	0.272 0.057(10)	0.289 0.066(10)	0.247 0.086(10)	0.325 0.055(10)
Cell Suspension Volume (mL)	7.2 0.3(10)	7.0 0.3(10)	7.2 0.4(10)	7.2 0.4(10)	7.2 0.3(10)	7.3 0.2(10)
Number of Cells in Half (x 10^6 cells/mL)	85.03 23.22(10)	83.16 36.67(10)	88.66 28.23(10)	96.80 40.05(10)	80.30 39.10(10)	120.95 38.87(10)
Total Number of Cells (x 10^8)	12.34 3.34(10)	12.44 5.92(10)	13.18 4.49(10)	14.03 5.81(10)	11.67 6.26(10)	17.47† 6.40(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

FIGURES

Figure 1
Representative Analytical Calibration Curve

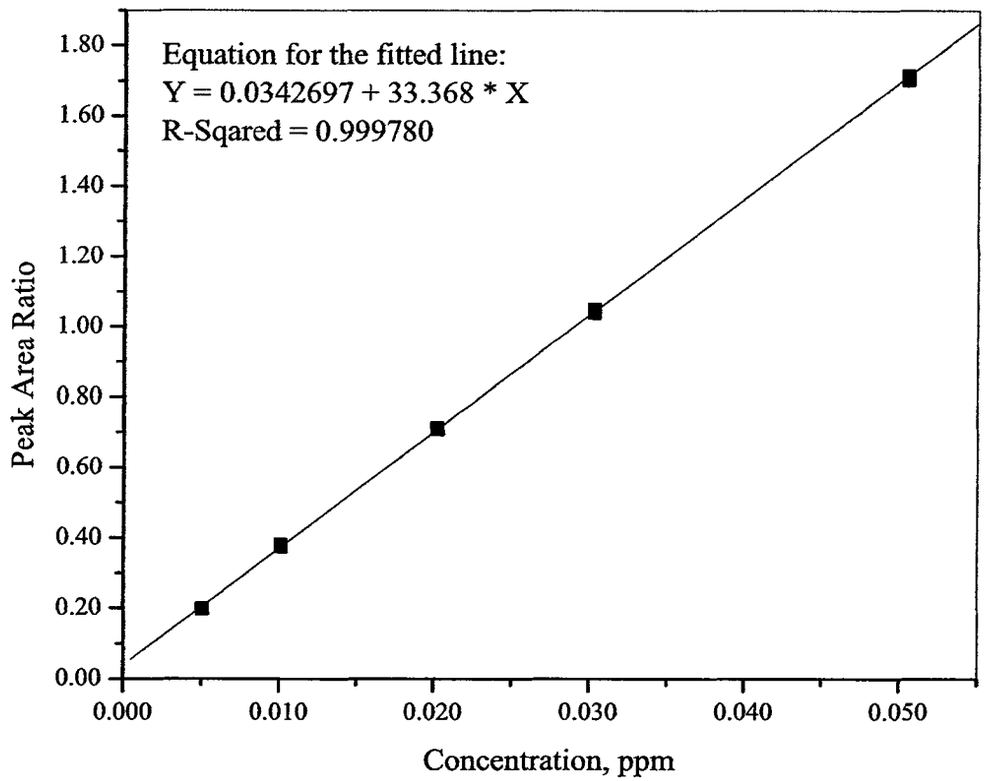


Figure 1: Calibration curve showing linear fit (line) to replicate peak area ratio measurements (squares) for matrix matched calibration solutions of APFO diluted over a concentration range of 0.00505 to 0.0505 ppm.

Figure 2
Representative LC/MS/MS Chromatograms

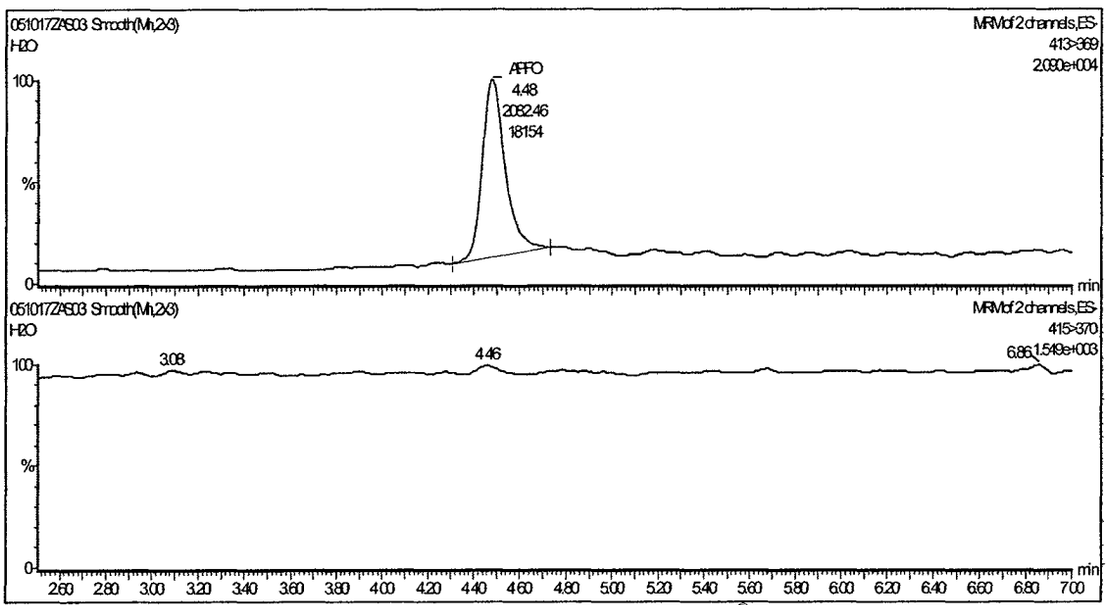


Figure 2a: Representative LC/MS/MS chromatogram of NANOpure® water used as the diluent in the study. Retention time for PFOA is approximately 4.5 minutes.

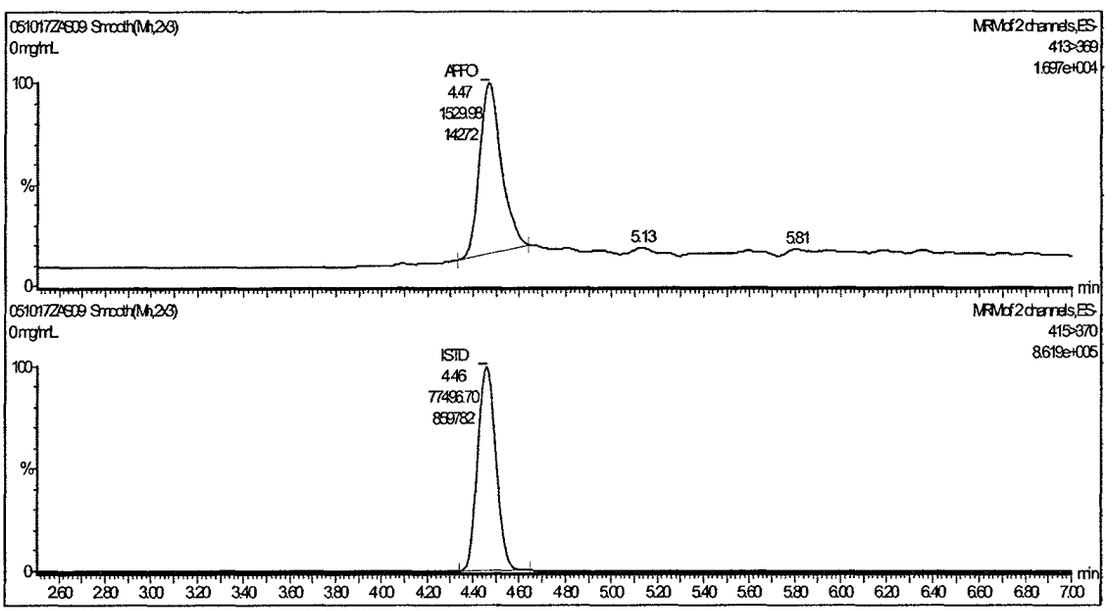


Figure 2b: Representative LC/MS/MS chromatogram of 0 mg/mL control sample. Retention time for PFOA is approximately 4.5 minutes.

Figure 2
Representative LC/MS/MS Chromatograms (Continued)

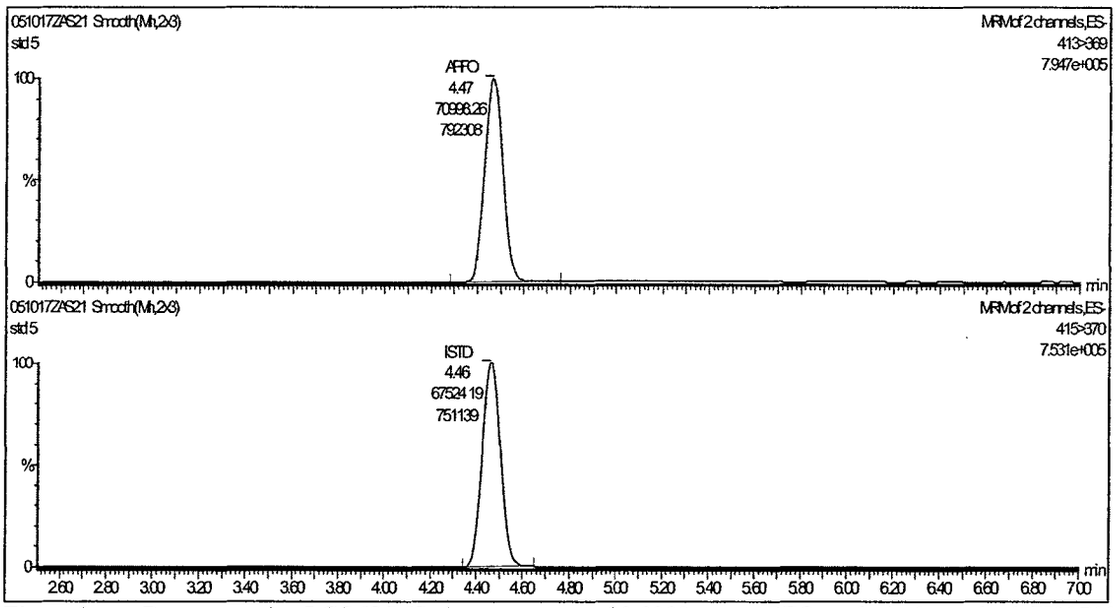


Figure 2c: Representative LC/MS/MS chromatogram of 0.0303 ppm APFO analytical standard (H22703-376) diluted with NANOpure® water after matrix correction.

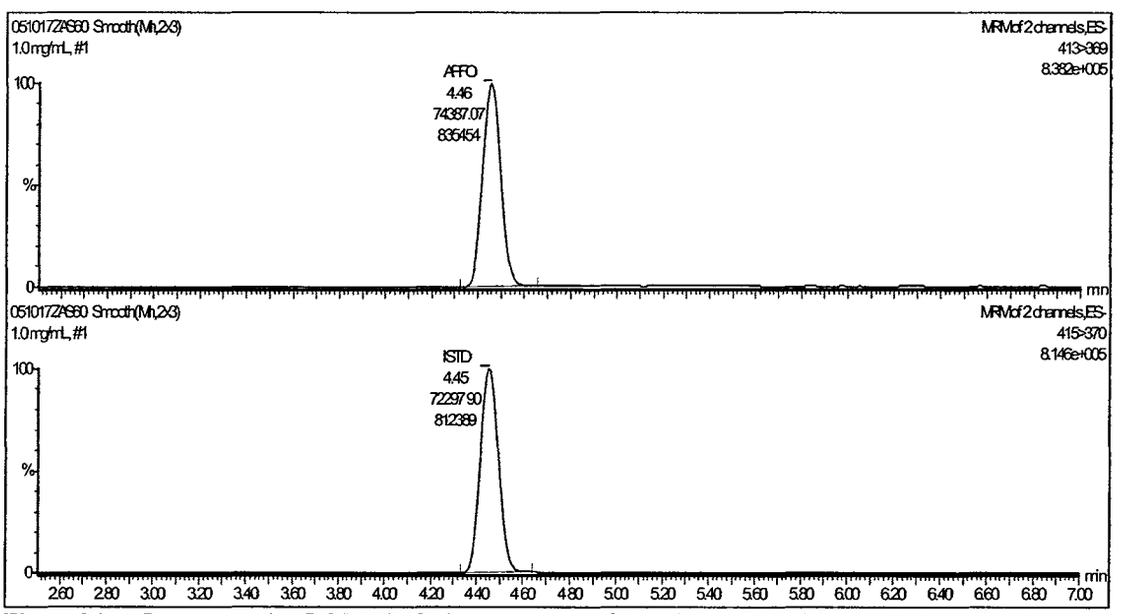


Figure 2d: Representative LC/MS/MS chromatogram of 1 mg/mL APFO dosing solution diluted to a nominal concentration of 0.03 mg/mL. The measured concentration of the representative solution is 0.979 mg/mL.

Figure 2
Representative LC/MS/MS Chromatograms (Continued)

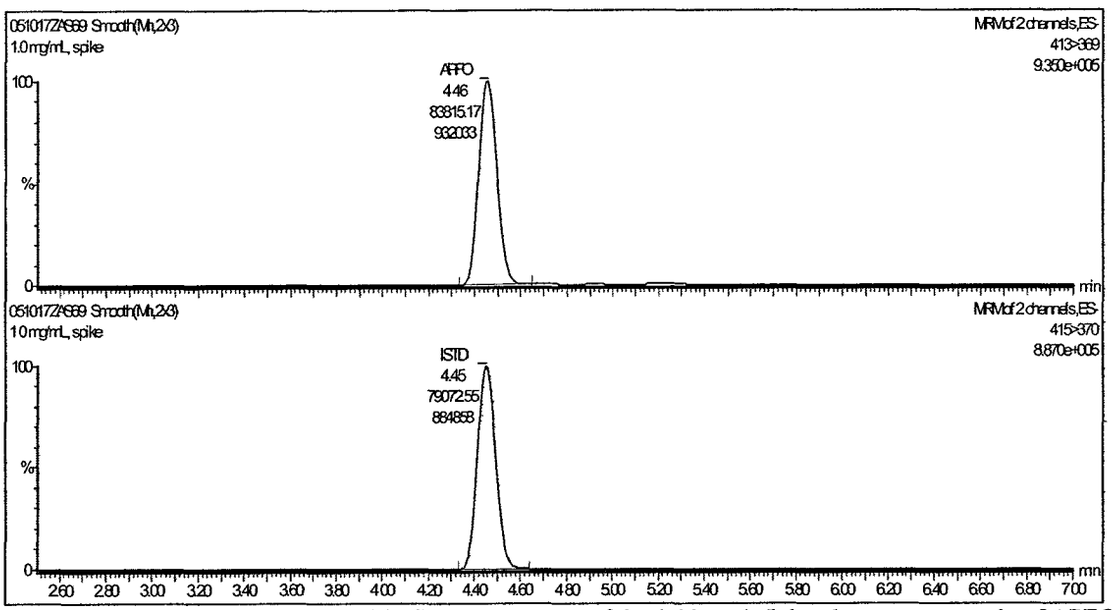
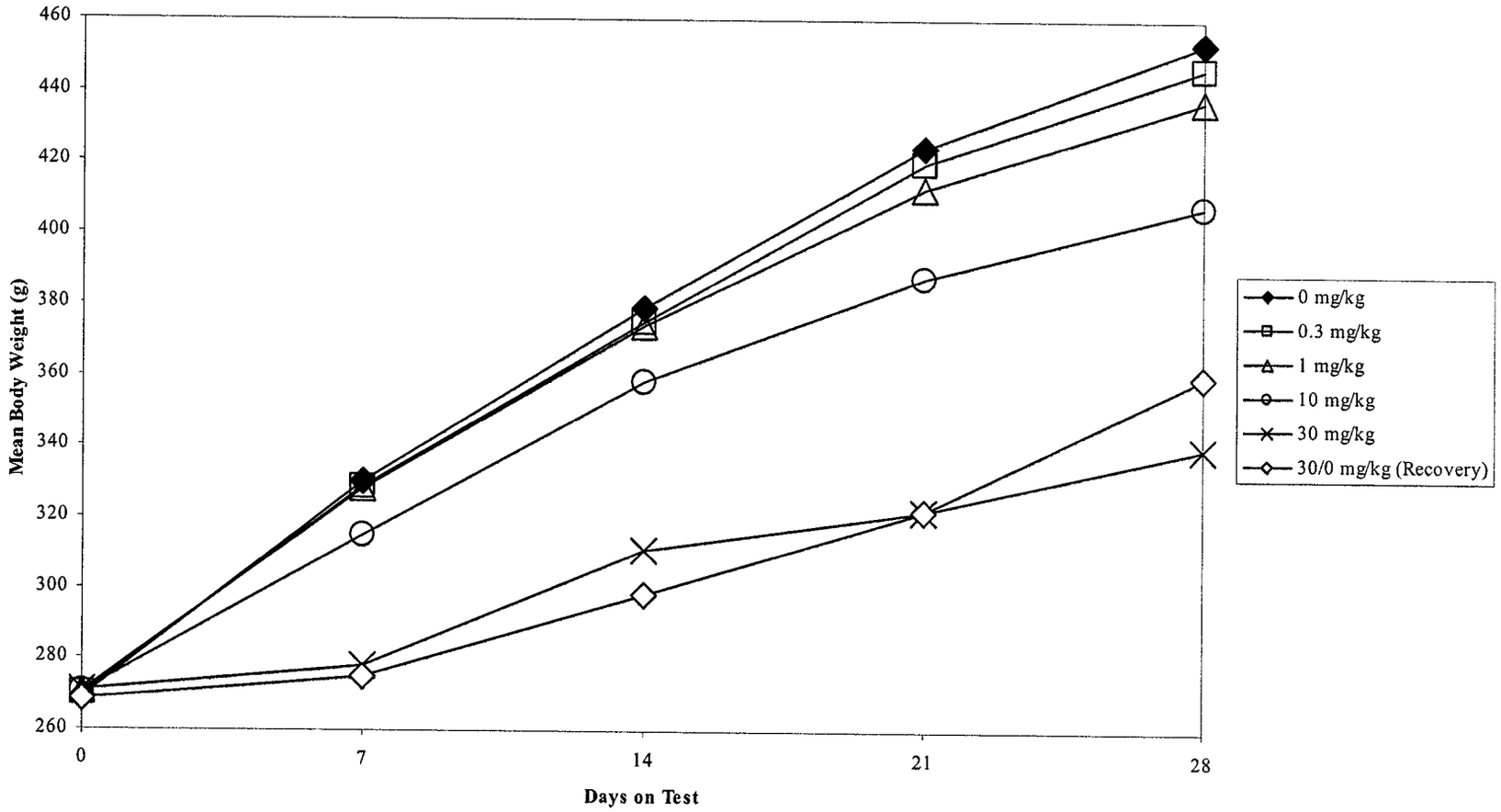


Figure 2e: Representative LC/MS/MS chromatogram of the 1.00 mg/mL level recovery sample of APFO diluted with NANOpure® water after matrix correction to a nominal concentration of 0.0300 ppm. The measured concentration of the representative recovery sample is 1.02 mg/mL.

Figure 3
Mean Body Weights of Male Rats



APPENDICES

Appendix A
Certificate of Analysis

Exygen RESEARCH
Precise Research. Proven Results.
3058 Research Drive
State College, PA 16801
T: 814.272.1039
exygen.com

Certificate of Analysis

CERTIFICATE OF ANALYSIS

This Certificate of Analysis fulfills the requirement for characterization of a test substance prior to a study subject to the GLP regulations. It documents the purity of the test substance. This work was conducted under TSCA Good Laboratory Practice Standards (40 CFR 792) and FIFRA Good Laboratory Practice Standards (40 CFR 160).

Designation of the Certified Material:
Compound: APFO (Linear)
Haskell Number: H27308

Analytical Data:
The Purity of the Certified Material was Established by LC/MS/MS

Purity: 19.5%

Last Date of Analysis: 07-November-2005
Re-certification Date: 07-November-2006

Origin of Certified Material:
E.I. du Pont de Nemours and Company
Wilmington, DE 19898
USA

Testing Facility/Performing Laboratory:
Exygen Research
3058 Research Drive
State College, PA 16801

Prepared By: _____ 11/15/05
Charles Simons Date
Study Director, Exygen Research

Facility Management: _____ for _____ 15-Nov-05
John Flaherty John Flaherty Date
Vice-President, Exygen Research

Appendix B
Individual Body Weights

INDIVIDUAL BODY WEIGHTS

EXPLANATORY NOTES

ABBREVIATIONS:

g - grams

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 3	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12
Male, I 0 mg/kg									
101	274.9	299.7	336.0	343.3	351.4	361.0	372.4	375.7	382.1
102	258.4	282.9	323.9	333.2	342.2	354.6	366.8	374.5	382.0
103	276.7	299.4	329.7	339.5	344.2	354.4	364.3	369.9	376.8
104	280.8	301.2	327.2	340.5	342.7	353.8	357.9	358.7	371.5
105	248.1	262.3	290.3	295.5	301.2	311.9	316.7	322.2	331.1
106	270.4	287.8	319.2	325.8	333.3	341.5	348.0	348.8	362.2
107	267.3	282.8	305.9	320.2	325.2	331.7	336.0	343.0	352.2
108	264.3	289.0	319.8	324.2	331.6	338.2	341.6	351.2	352.9
109	287.6	304.9	342.0	351.9	358.0	372.1	376.7	381.9	388.8
110	262.2	281.0	313.0	323.7	328.6	340.3	346.7	353.1	360.1
Male, III 0.3 mg/kg									
301	275.5	300.8	336.1	342.5	350.5	361.0	364.7	374.1	380.6
302	262.8	288.5	321.6	333.3	338.7	353.3	360.7	366.9	376.2
303	283.5	304.9	338.8	350.9	358.6	371.9	373.1	386.4	397.7
304	277.4	293.9	321.9	324.0	326.9	340.3	339.9	347.4	353.8
305	247.4	269.0	298.6	306.5	309.4	323.1	328.4	333.6	340.1
306	272.3	297.1	333.1	339.0	340.8	356.7	361.6	371.4	377.8
307	272.5	286.8	315.2	321.2	324.1	336.0	340.1	340.7	353.9
308	265.4	275.1	308.6	311.1	317.6	328.0	332.0	333.9	339.5
309	284.9	304.4	339.4	342.2	351.9	366.2	365.6	373.2	389.0
310	261.5	276.8	307.2	314.0	316.7	329.2	330.6	336.8	346.7
Male, V 1 mg/kg									
501	266.9	284.9	320.1	331.2	337.0	349.5	349.4	360.1	375.9
502	259.7	278.2	308.9	317.5	327.4	332.2	341.4	341.8	353.6
503	276.2	302.9	336.9	346.3	354.1	365.1	369.1	375.2	385.5
504	283.6	297.6	336.0	346.2	354.8	367.5	372.7	376.6	385.7
505	245.0	264.5	296.4	300.5	300.8	311.7	316.0	318.6	326.1
506	271.9	287.1	320.2	326.5	326.4	341.7	343.6	347.8	356.4
507	274.5	284.0	309.4	314.1	322.5	327.7	332.7	336.1	342.3
508	271.3	292.0	321.6	329.3	335.9	347.4	352.0	359.4	366.9
509	295.2	313.7	353.3	359.6	370.1	379.8	386.1	396.5	406.1
510	261.8	277.2	305.1	310.6	317.3	327.4	327.2	334.2	340.9

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 3	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12
Male, VII 10 mg/kg									
701	270.1	284.6	305.9	308.8	313.9	320.2	325.7	328.0	326.7
702	252.6	274.2	305.9	306.3	313.8	323.6	333.8	340.4	348.1
703	278.4	298.0	322.2	323.0	334.5	342.6	349.9	346.9	354.6
704	285.3	302.5	306.3	314.0	324.5	333.5	330.2	327.1	332.2
705	243.3	257.6	270.4	273.3	273.9	289.0	298.6	302.3	313.9
706	273.1	296.0	321.9	325.2	334.5	346.2	353.1	358.2	372.8
707	275.2	295.5	325.0	334.7	338.4	349.9	356.4	360.0	370.6
708	270.7	287.1	307.0	309.3	320.3	323.8	336.5	340.9	345.3
709	290.6	307.5	328.1	336.3	346.7	354.0	364.9	369.0	377.1
710	265.4	280.3	315.3	316.0	317.9	331.5	337.9	340.6	349.6
Male, IX 30 mg/kg									
901	269.5	233.8	201.9	223.0	242.9	250.8	244.5	264.6	275.1
902	261.2	225.3	186.8	212.2	231.4	241.0	254.4	257.3	263.3
903	278.1	268.2	304.0	307.6	315.5	328.1	335.8	337.0	349.3
904	277.8	270.6	293.9	293.0	295.7	299.6	298.6	296.1	296.9
905	254.4	262.0	298.4	301.6	305.7	312.9	315.1	315.4	322.0
906	277.7	261.0	217.9	246.5	257.5	267.4	276.0	280.8	291.5
907	274.6	261.7	294.5	309.4	312.0	318.5	320.5	326.8	330.7
908	267.2	249.8	279.2	284.0	288.4	290.6	297.2	306.4	310.8
909	284.0	278.1	315.6	317.1	316.6	322.1	327.5	335.8	339.5
910	268.0	249.2	281.7	285.2	291.4	300.8	303.1	297.8	304.0
Male, XI 30/0 mg/kg (Recovery)									
1101	263.1	254.2	284.3	287.6	286.5	273.9	275.1	287.5	293.6
1102	257.0	238.0	225.8	243.3	255.1	260.8	267.2	286.6	289.9
1103	275.3	274.1	307.1	313.2	315.4	316.0	322.5	324.1	326.7
1104	286.3	280.8	313.0	325.2	324.4	320.2	322.3	329.8	342.8
1105	259.9	248.8	270.9	276.6	277.0	284.0	287.7	293.4	301.8
1106	269.4	272.4	314.6	319.2	327.1	335.7	346.0	346.0	354.8
1107	267.3	254.7	287.1	284.2	285.1	290.0	290.4	285.6	287.4
1108	272.9	259.5	279.5	273.0	270.9	274.6	267.8	261.2	266.8
1109	271.7	227.5	173.0	162.8	171.5	193.5	213.0	228.1	225.8
1110	260.9	256.7	263.3	264.9	275.9	283.0	280.9	276.2	283.0

Individual Body Weights

	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21
Male, I 0 mg/kg									
101	393.0	392.2	404.3	410.1	420.4	430.5	438.9	442.1	453.1
102	388.3	396.2	405.5	419.6	418.2	433.8	439.8	441.8	445.2
103	384.8	385.3	396.5	403.5	410.8	428.0	436.6	440.8	445.8
104	373.9	385.4	386.0	390.9	405.7	404.9	415.8	418.4	425.1
105	337.0	346.4	351.7	357.3	361.6	379.4	380.4	383.9	386.2
106	364.0	369.2	374.3	380.9	383.8	392.5	396.2	403.0	412.1
107	354.3	360.2	366.4	366.3	375.7	386.9	390.5	394.8	401.1
108	357.3	362.5	371.3	375.4	381.4	391.6	397.0	398.9	402.5
109	403.8	414.7	417.8	421.8	431.3	443.6	446.6	450.5	454.4
110	372.1	375.5	381.7	382.0	386.8	396.9	402.3	409.1	414.7
Male, III 0.3 mg/kg									
301	381.3	385.8	393.5	400.8	406.3	416.6	421.7	424.6	425.7
302	379.9	392.0	393.0	405.6	402.9	419.1	418.5	429.7	430.2
303	397.1	404.2	414.6	421.6	429.6	438.9	447.5	454.3	461.8
304	352.9	365.7	373.4	375.0	378.5	393.2	397.6	401.8	405.7
305	341.7	353.9	360.2	360.8	370.2	381.5	384.9	387.9	396.5
306	382.0	388.4	402.1	402.7	409.8	420.1	424.7	432.1	436.8
307	359.3	362.6	374.6	374.1	380.2	389.8	397.1	399.5	408.7
308	346.1	348.6	354.9	354.9	357.6	374.0	371.1	381.1	384.5
309	389.3	396.3	402.7	410.9	418.2	427.3	437.5	440.9	446.0
310	347.8	352.1	364.4	366.6	371.0	387.2	392.2	392.6	400.7
Male, V 1 mg/kg									
501	375.0	375.8	389.8	393.8	404.5	408.3	414.9	421.0	424.4
502	357.8	359.7	362.9	369.1	370.9	386.4	390.0	390.3	390.1
503	390.9	402.0	407.0	411.1	416.8	444.0	433.6	432.9	446.5
504	390.7	399.7	402.1	406.9	413.8	423.7	426.5	434.6	440.6
505	328.1	334.9	336.8	339.6	346.3	353.6	360.0	363.0	368.2
506	367.5	367.0	377.3	376.1	383.4	396.0	399.3	409.2	408.6
507	350.5	355.4	357.7	360.2	360.3	374.4	374.3	377.6	376.0
508	372.6	380.6	383.8	390.1	391.9	405.6	410.6	416.5	424.3
509	409.4	413.5	424.7	436.2	437.1	459.5	467.4	466.1	470.4
510	337.2	348.2	356.1	355.7	362.8	368.7	379.1	377.0	376.5

Individual Body Weights

	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21
Male, VII 10 mg/kg									
701	328.8	337.9	342.3	345.0	345.0	355.0	353.6	361.0	358.6
702	350.8	364.0	364.9	370.4	375.8	382.4	385.1	391.4	392.6
703	362.0	371.0	374.5	375.9	378.9	396.9	395.8	397.0	398.4
704	336.3	342.4	344.1	348.4	350.4	358.2	364.6	369.3	369.2
705	319.0	321.1	331.6	330.7	331.2	337.1	334.1	338.0	333.2
706	375.3	378.1	381.4	396.1	395.8	407.9	410.5	423.8	419.0
707	372.1	380.6	385.3	387.9	394.5	409.7	418.9	413.0	424.3
708	342.8	342.2	354.2	350.5	355.4	362.3	365.6	366.7	367.9
709	380.4	384.1	388.4	399.0	402.1	403.6	408.7	417.8	421.5
710	360.2	358.7	364.6	371.9	364.9	379.6	381.1	389.2	390.6
Male, IX 30 mg/kg									
901	281.1	261.5	244.9	229.4	215.8	208.4	234.3	248.5	253.1
902	272.9	282.5	279.2	288.5	292.8	298.1	302.0	296.6	297.4
903	348.9	355.4	357.9	367.0	368.8	378.4	381.1	383.5	392.5
904	296.8	297.9	298.1	294.3	289.1	301.6	301.5	301.9	294.6
905	324.3	320.1	321.5	328.3	326.0	336.9	339.1	336.4	337.2
906	297.6	299.4	312.2	304.5	307.4	315.1	315.5	321.0	325.1
907	329.0	331.1	340.9	340.9	340.2	349.1	344.0	339.4	341.7
908	309.1	307.8	309.8	311.0	312.7	317.1	318.9	317.0	319.1
909	341.1	345.2	350.3	355.9	363.2	365.2	366.8	359.9	353.5
910	304.6	306.0	308.9	303.6	306.6	306.7	304.4	306.9	305.3
Male, XI 30/0 mg/kg (Recovery)									
1101	300.9	298.5	312.5	312.9	320.4	317.4	324.8	329.0	334.0
1102	296.9	298.4	312.8	309.5	312.3	328.8	327.1	338.9	333.1
1103	329.2	329.4	339.3	332.2	334.9	341.7	342.6	344.6	343.0
1104	353.9	355.8	354.0	359.6	360.9	375.8	374.9	375.0	370.5
1105	307.4	312.0	309.0	319.2	319.4	321.3	324.1	328.0	324.4
1106	358.8	355.9	368.7	369.1	374.8	383.1	384.9	387.4	388.6
1107	290.6	291.7	297.2	300.7	297.9	311.2	308.6	314.3	308.7
1108	263.9	270.1	277.7	272.3	279.6	280.8	283.2	284.4	282.7
1109	197.7	181.2	173.9	199.9	211.0	219.1	213.0	197.3	225.9
1110	285.2	292.0	293.0	296.5	297.0	307.0	309.1	315.4	311.3

Individual Body Weights

	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27	Body Weight g Day 28
Male, I 0 mg/kg							
101	454.7	464.8	463.6	478.2	480.1	479.0	483.9
102	452.1	457.7	462.8	472.2	476.8	471.6	475.9
103	446.2	455.6	454.3	468.4	470.7	474.3	476.3
104	430.5	426.4	438.0	448.7	451.7	451.9	454.4
105	393.4	399.0	405.5	405.5	411.0	412.2	417.4
106	416.6	417.8	422.2	429.9	433.7	430.4	440.5
107	400.3	408.8	409.5	413.6	413.7	418.1	420.6
108	409.6	414.9	416.3	425.6	430.4	429.6	432.4
109	457.0	463.1	470.0	475.8	479.8	481.2	489.3
110	420.5	425.2	430.3	435.7	440.4	442.5	442.8
Male, III 0.3 mg/kg							
301	431.6	438.7	437.1	444.3	447.7	454.2	452.7
302	435.2	440.5	447.1	454.8	453.7	456.3	463.7
303	467.3	471.0	480.3	489.7	492.7	496.0	502.4
304	407.5	407.6	417.4	420.1	426.9	423.2	419.8
305	397.9	400.6	408.6	416.9	415.4	416.5	421.4
306	439.8	443.4	447.5	461.1	462.0	465.6	467.1
307	411.1	415.9	422.5	425.5	432.7	436.3	434.4
308	388.1	392.9	394.8	401.0	405.8	404.0	402.9
309	448.5	456.4	460.4	473.8	473.8	476.0	475.1
310	406.3	409.6	416.6	421.0	421.6	423.6	426.3
Male, V 1 mg/kg							
501	429.4	433.2	431.8	438.3	442.8	443.9	450.2
502	401.3	409.4	406.2	413.1	415.9	414.9	418.0
503	445.7	453.2	455.6	459.9	463.9	464.8	464.6
504	448.3	451.5	458.3	466.7	470.4	467.6	472.4
505	372.3	373.9	376.6	384.5	385.5	384.6	389.0
506	412.6	416.8	421.0	424.9	428.9	430.3	433.3
507	380.5	383.5	380.2	388.9	390.3	387.8	390.6
508	427.5	425.2	423.1	426.7	429.5	433.0	433.4
509	478.7	481.8	488.6	502.7	505.4	507.0	512.1
510	389.4	391.0	390.2	402.3	405.6	406.7	408.6

Individual Body Weights

	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27	Body Weight g Day 28
Male, VII 10 mg/kg							
701	363.8	368.4	366.0	375.7	378.7	378.7	380.2
702	392.4	404.6	399.6	413.5	422.9	422.8	420.3
703	398.0	408.1	403.1	406.3	403.6	401.1	406.9
704	374.6	373.9	377.2	375.3	372.5	381.9	382.2
705	339.6	343.7	341.7	344.3	345.5	345.1	345.9
706	425.8	429.4	426.5	433.3	451.8	445.7	452.5
707	434.2	437.4	436.5	443.4	447.2	446.6	450.6
708	372.0	378.0	375.1	376.1	377.2	377.1	384.7
709	424.6	431.8	423.8	434.6	440.7	441.5	441.5
710	393.5	400.9	403.5	411.0	409.4	415.9	410.4
Male, IX 30 mg/kg							
901	261.0	271.7	281.9	292.3	295.4	296.7	292.6
902	302.8	300.6	302.0	307.6	307.4	313.9	313.7
903	395.3	399.1	401.2	406.7	416.8	413.4	418.0
904	296.8	299.4	301.0	310.5	311.4	308.0	309.7
905	344.1	346.2	337.8	350.2	353.1	351.8	353.2
906	327.5	329.9	323.0	334.2	338.1	337.3	333.2
907	342.1	347.8	348.2	350.7	353.3	352.3	356.9
908	318.0	321.3	326.1	327.3	333.3	331.1	333.4
909	358.7	353.8	350.5	363.6	363.1	366.0	367.1
910	306.3	306.3	309.5	316.0	316.0	312.3	317.7
Male, XI 30/0 mg/kg (Recovery)							
1101	338.3	338.0	338.7	352.6	353.1	352.0	352.5
1102	338.5	338.4	346.3	356.6	360.6	358.9	366.7
1103	339.3	348.0	351.0	357.5	361.7	364.8	366.1
1104	378.3	389.7	394.4	408.2	417.1	418.4	424.4
1105	330.7	333.2	341.9	347.9	352.9	359.8	361.0
1106	399.3	400.2	409.4	416.3	421.5	418.4	421.9
1107	314.3	313.3	323.2	327.9	337.6	334.7	342.1
1108	284.1	288.0	286.1	294.3	299.4	300.6	304.0
1109	233.5	247.7	258.8	274.6	289.0	297.4	309.1
1110	315.9	316.0	322.7	332.6	339.3	342.0	349.8

Appendix C
Individual Food Consumption

INDIVIDUAL FOOD CONSUMPTION

EXPLANATORY NOTES

ABBREVIATIONS:

Cons. - consumption
g/anm/day - grams of food consumed per animal per day

Individual Food Consumption

	Food Cons. g/anm/day Day 7	Food Cons. g/anm/day Day 14	Food Cons. g/anm/day Day 21	Food Cons. g/anm/day Day 28
Male, I 0 mg/kg				
101	30.2	30.6	31.7	31.1
102	29.3	31.5	32.1	30.5
103	30.2	28.9	32.2	31.0
104	27.6	27.9	28.1	30.8
105	24.7	25.2	26.1	26.8
106	30.0	29.1	30.8	29.9
107	27.6	27.6	28.3	28.0
108	29.6	28.1	29.1	30.2
109	30.3	33.5	32.0	31.9
110	28.1	29.2	30.1	32.2
Male, III 0.3 mg/kg				
301	29.8	29.3	29.2	31.2
302	29.0	30.9	29.5	30.5
303	30.1	31.0	33.6	34.9
304	27.5	26.8	27.7	27.6
305	25.7	26.1	27.3	26.6
306	30.2	32.9	32.8	30.6
307	25.5	26.1	27.5	27.9
308	25.3	26.2	25.4	26.6
309	30.0	31.1	31.1	32.3
310	26.9	26.9	28.0	28.8
Male, V 1 mg/kg				
501	28.5	28.9	29.9	28.6
502	28.3	28.8	27.8	28.4
503	29.6	30.1	29.8	27.0
504	31.4	32.9	30.6	31.8
505	27.5	26.6	25.1	26.4
506	27.4	28.4	29.3	29.1
507	24.1	24.1	22.9	23.7
508	30.1	28.8	30.0	28.2
509	31.2	32.5	33.2	33.6
510	27.3	26.2	26.7	28.0

Individual Food Consumption

	Food Cons. g/anm/day Day 7	Food Cons. g/anm/day Day 14	Food Cons. g/anm/day Day 21	Food Cons. g/anm/day Day 28
Male, VII 10 mg/kg				
701	27.8	26.6	27.2	28.8
702	25.5	29.8	30.2	30.1
703	26.9	30.0	30.9	27.1
704	25.3	25.9	26.6	26.1
705	24.0	29.0	26.1	26.7
706	27.2	31.1	31.2	30.9
707	29.0	31.8	34.7	33.9
708	24.4	26.8	26.9	27.3
709	26.0	29.7	28.1	29.3
710	27.4	30.3	30.0	31.0
Male, IX 30 mg/kg				
901	9.2	24.6	11.9	25.7
902	8.6	27.0	23.5	24.8
903	23.4	30.5	29.2	29.7
904	24.7	23.4	22.2	23.9
905	24.7	25.3	22.9	24.0
906	14.5	35.3	30.3	29.0
907	25.0	26.2	24.2	26.4
908	22.2	29.3	25.0	28.5
909	24.5	30.9	28.7	26.5
910	23.9	26.8	22.3	26.6
Male, XI 30/0 mg/kg (Recovery)				
1101	24.2	23.2	26.2	24.4
1102	13.9	31.9	27.2	26.1
1103	25.8	28.6	26.8	25.8
1104	23.7	28.6	27.0	29.7
1105	23.0	25.1	22.3	25.1
1106	26.9	29.2	28.9	29.2
1107	22.1	22.2	24.7	25.9
1108	22.8	21.0	23.5	23.1
1109	5.1	15.8	20.4	32.0
1110	21.4	27.1	27.9	28.2

Appendix D
Individual Daily Animal Health Observations

Individual Daily Animal Health Observations

Sex	Group	Animal	Observation	Days
M	I	101	General observation, No Abnormality Detected	0-28
M	I	102	General observation, No Abnormality Detected	0-28
M	I	103	General observation, No Abnormality Detected	0-28
M	I	104	General observation, No Abnormality Detected	0-28
M	I	105	General observation, No Abnormality Detected	0-28
M	I	106	General observation, No Abnormality Detected	0-28
M	I	107	General observation, No Abnormality Detected	0-28
M	I	108	General observation, No Abnormality Detected	0-28
M	I	109	General observation, No Abnormality Detected	0-28
M	I	110	General observation, No Abnormality Detected	0-28
M	III	301	General observation, No Abnormality Detected	0-28
M	III	302	General observation, No Abnormality Detected	0-28
M	III	303	General observation, No Abnormality Detected	0-28
M	III	304	General observation, No Abnormality Detected	0-28
M	III	305	General observation, No Abnormality Detected	0-28
M	III	306	General observation, No Abnormality Detected	0-28
M	III	307	General observation, No Abnormality Detected	0-28
M	III	308	General observation, No Abnormality Detected	0-28
M	III	309	General observation, No Abnormality Detected	0-28
M	III	310	General observation, No Abnormality Detected	0-28
M	V	501	General observation, No Abnormality Detected	0-28
M	V	502	General observation, No Abnormality Detected	0-28
M	V	503	General observation, No Abnormality Detected	0-28
M	V	504	General observation, No Abnormality Detected	0-28
M	V	505	General observation, No Abnormality Detected	0-28
M	V	506	General observation, No Abnormality Detected	0-28
M	V	507	General observation, No Abnormality Detected	0-28
M	V	508	General observation, No Abnormality Detected	0-28
M	V	509	General observation, No Abnormality Detected	0-28
M	V	510	General observation, No Abnormality Detected	0-28

Individual Daily Animal Health Observations

Sex	Group	Animal	Observation	Days
M	VII	701	General observation, No Abnormality Detected	0-28
M	VII	702	General observation, No Abnormality Detected	0-28
M	VII	703	General observation, No Abnormality Detected	0-28
M	VII	704	General observation, No Abnormality Detected	0-28
M	VII	705	General observation, No Abnormality Detected	0-28
M	VII	706	General observation, No Abnormality Detected	0-28
M	VII	707	General observation, No Abnormality Detected	0-28
M	VII	708	General observation, No Abnormality Detected	0-28
M	VII	709	General observation, No Abnormality Detected	0-28
M	VII	710	General observation, No Abnormality Detected	0-28
M	IX	901	General observation, No Abnormality Detected	0-3,8-17,19-28
			Feces, Absent	18
			Comments, decreased feces	4-7
			Not Eating	18
M	IX	902	General observation, No Abnormality Detected	0-3,8-28
			Comments, decreased feces	4-7
			Not Eating	4-7
M	IX	903	General observation, No Abnormality Detected	0-3,5-28
			Not Eating	4
M	IX	904	General observation, No Abnormality Detected	0-28
M	IX	905	General observation, No Abnormality Detected	0-28
M	IX	906	General observation, No Abnormality Detected	0-28
M	IX	907	General observation, No Abnormality Detected	0-28
M	IX	908	General observation, No Abnormality Detected	0-28
M	IX	909	General observation, No Abnormality Detected	0-28
M	IX	910	General observation, No Abnormality Detected	0-28
M	XI	1101	General observation, No Abnormality Detected	0-3,5-28
			Not Eating	4
M	XI	1102	General observation, No Abnormality Detected	0-4,8-28
			Comments, decreased feces	5-7
M	XI	1103	General observation, No Abnormality Detected	0-28
M	XI	1104	General observation, No Abnormality Detected	0-28
M	XI	1105	General observation, No Abnormality Detected	0-28
M	XI	1106	General observation, No Abnormality Detected	0-28
M	XI	1107	General observation, No Abnormality Detected	0-28
M	XI	1108	General observation, No Abnormality Detected	0-28
M	XI	1109	General observation, No Abnormality Detected	0-3,11-28
			Feces, Absent	4-5
			Stain Fur/Skin, Inguen, Brown	9-10
			Stain Fur/Skin, Inguen, Red	5
			Wet Fur, Inguen	5
			Not Eating	4-5
M	XI	1110	General observation, No Abnormality Detected	0-28

Appendix E
Individual Detailed Clinical Observations and Mortality Records

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	I	101	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	102	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	103	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	104	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	105	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	106	General observation, No Abnormality Detected	0-7
			Hair Loss, Forelimb, Bilateral	14-29
			Sacrificed by design	29
M	I	107	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	108	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	109	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	110	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	301	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	302	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	303	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	304	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	305	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	306	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	307	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	308	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	309	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	310	General observation, No Abnormality Detected	0-29
M			Sacrificed by design	29
M	V	501	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	502	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	503	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	504	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	505	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	506	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	507	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	508	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	509	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	510	General observation, No Abnormality Detected	0
			Hair Loss, Forelimb, Bilateral	7-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	VII	701	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	702	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	703	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	704	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	705	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	706	General observation, No Abnormality Detected	0-14
			Hair Loss, Forepaw, Bilateral	21-29
			Sacrificed by design	29
M	VII	707	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	708	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	709	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	710	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	901	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	902	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	903	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	904	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	905	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	906	General observation, No Abnormality Detected	0
			Hair Loss, Abdomen, Bilateral	7-29
			Hair Loss, Forelimb, Bilateral	21-29
			Hair Loss, Hindlimb, Bilateral	21-29
			Sacrificed by design	29
M	IX	907	General observation, No Abnormality Detected	0-7
			Hair Loss, Forepaw, Bilateral	14-29
			Sacrificed by design	29
M	IX	908	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	909	General observation, No Abnormality Detected	0-14
			Hair Loss, Forelimb, Bilateral	21-29
			Hair Loss, Forepaw, Bilateral	21-29
			Sacrificed by design	29
M	IX	910	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	XI	1101	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1102	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1103	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1104	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1105	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1106	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1107	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1108	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1109	General observation, No Abnormality Detected	0,11-29
			Lethargic	6-7
			Carriage, High	6-7
			Feces, Absent	6-8
			Stain Fur/Skin, Abdomen, Red	8
			Stain Fur/Skin, Forepaw, Bilateral, Red	6-7
			Stain Fur/Skin, Inguen, Red	8
			Stain Fur/Skin, Perineum, Red	8
			Stain Fur/Skin, Ventral body, Red	6-7
			Stain Fur/Skin, Perinasal, Red	6-7
			Stain Fur/Skin, Perioral, Red	6-7
			Wet Fur, Ventral body, Ventral	6
			Not Eating	6-7
			Sacrificed by design	29
M	XI	1110	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Appendix F
Individual Animal Clinical Pathology Data

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

General:

Adeq	-	adequate
CLOT or Clot	-	sample clotted
Decr	-	decreased
Mod	-	moderate
NP	-	not taken, not performed, or results not valid
OK	-	sample condition OK for testing

Individual Hematology Values:

COND	-	sample condition
RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular (cell) volume
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell

Individual Red Blood Cell Morphology Values:

ANIS	-	anisocytosis
MIC	-	microcytes
MAC	-	macrocytes
POLY	-	polychromasia
HYPO	-	hypochromasia
ECHI	-	echinocytes
ACAN	-	acanthocytes
TARG	-	target cells
RX	-	rouleaux
HJB	-	Howell-Jolly body
-	-	not observed

Individual White Blood Cell / Platelet Morphology Values:

SM	-	smudge white blood cells
TOX	-	toxic neutrophils
DB	-	Döhle bodies
VC	-	vacuolated cytoplasm
BC	-	basophilic cytoplasm
PCE	-	platelet clumps / estimate
GP	-	giant platelets
BP	-	bizarre platelets
-	-	not observed

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Individual Clinical Chemistry Values:

HEM	-	hemolysis
LIP	-	lipemia
ICT	-	icterus
CHOL	-	cholesterol
TRIG	-	triglycerides
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
HDL	-	high-density lipoprotein cholesterol
NHDL	-	non-high-density lipoprotein cholesterol
SCORT	-	serum corticosterone

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:
the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

Only positive findings were recorded for special observations (e.g., additional cell types) or observations marked other.

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29				
Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
101	OK	7.77	14.6	45.6	58.7	18.8	32.0	11.5	200.3	NP
102	OK	7.53	15.0	47.1	62.6	19.9	31.8	11.8	196.6	1006
103	OK	7.85	15.4	48.3	61.6	19.6	31.9	11.6	208.2	NP
104	OK	7.84	15.1	45.5	58.0	19.2	33.1	11.0	194.3	1119
105	OK	7.32	14.8	46.4	63.4	20.3	32.0	11.0	160.5	1261
106	OK	7.48	14.8	45.8	61.2	19.8	32.3	11.8	198.6	1207
107	CLOT	NP	NP	NP	NP	NP	NP	NP	NP	NP
108	OK	7.90	15.1	45.9	58.1	19.2	33.0	11.9	164.5	NP
109	OK	7.59	14.6	45.1	59.5	19.3	32.4	11.7	182.1	968
110	OK	7.67	14.8	45.9	59.9	19.4	32.3	11.6	180.9	976

Male,	Group	III	0.3	mg/kg	Day	29				
Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
301	OK	7.87	15.6	48.3	61.4	19.8	32.2	11.9	169.0	1042
302	OK	7.40	14.5	44.7	60.3	19.6	32.5	12.1	152.6	940
303	OK	8.15	15.4	47.7	58.5	18.9	32.2	11.4	166.7	1104
304	OK	8.11	14.9	45.9	56.6	18.4	32.5	11.8	189.9	1114
305	OK	7.50	14.6	45.0	59.9	19.4	32.4	11.2	148.8	1064
306	OK	7.31	14.5	44.6	61.0	19.9	32.6	11.0	158.0	1080
307	OK	7.57	13.9	43.5	57.5	18.4	31.9	10.8	147.4	1096
308	OK	7.61	14.6	44.6	58.6	19.2	32.8	10.7	180.3	1052
309	OK	7.45	14.5	44.4	59.5	19.4	32.6	11.8	185.7	1167
310	OK	7.17	14.7	45.6	63.5	20.4	32.2	11.6	206.3	923

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29				
Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
501	OK	7.96	15.2	48.3	60.7	19.1	31.4	12.1	163.1	NP
502	OK	8.05	15.8	48.3	59.9	19.7	32.8	12.3	207.6	872
503	OK	7.23	13.9	42.9	59.4	19.2	32.3	11.3	158.2	1112
504	OK	7.33	15.0	46.1	62.9	20.5	32.5	11.5	140.3	1166
505	OK	7.30	14.5	45.7	62.6	19.8	31.7	11.6	197.9	NP
506	OK	7.68	14.3	44.3	57.7	18.6	32.2	11.8	161.5	1159
507	OK	7.58	14.6	44.7	59.0	19.3	32.6	11.6	166.7	1120
508	OK	7.54	15.0	47.1	62.4	19.8	31.8	11.3	170.6	NP
509	OK	7.31	14.2	44.1	60.3	19.5	32.3	12.0	210.8	1135
510	OK	8.03	14.6	44.9	55.9	18.2	32.5	11.7	197.9	NP

Male,	Group	VII	10	mg/kg	Day	29				
Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
701	OK	7.98	13.7	43.6	54.7	17.2	31.4	12.7	210.5	981
702	OK	7.44	13.9	44.0	59.2	18.6	31.5	12.2	235.8	1038
703	OK	7.09	13.1	40.4	56.9	18.5	32.5	13.8	233.8	NP
704	OK	6.10	12.0	37.4	61.3	19.6	32.0	12.3	152.7	352
705	OK	7.48	13.5	43.1	57.6	18.1	31.4	12.4	123.0	NP
706	OK	7.24	13.5	42.7	59.0	18.7	31.7	13.6	257.1	1182
707	OK	7.31	14.7	45.9	62.7	20.1	32.1	11.9	195.8	NP
708	OK	7.65	14.2	43.8	57.2	18.6	32.5	12.2	154.9	1022
709	OK	7.54	13.5	43.3	57.4	17.9	31.2	13.7	248.5	1350
710	OK	7.00	13.3	41.6	59.4	18.9	31.9	12.7	232.4	1380

Individual Animal Clinical Pathology Data

Male, Group IX 30 mg/kg Day 29

Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
901	OK	7.44	13.3	42.6	57.2	17.9	31.2	14.6	280.3	NP
902	OK	7.22	13.5	41.1	56.9	18.7	32.8	13.2	206.0	1027
903	OK	6.85	13.3	42.0	61.3	19.4	31.7	12.1	178.4	1081
904	OK	8.72	14.8	45.8	52.5	17.0	32.4	12.7	152.4	NP
905	OK	7.13	13.5	42.6	59.8	19.0	31.8	12.4	198.0	1280
906	OK	8.08	14.4	44.9	55.6	17.8	32.1	12.8	156.9	998
907	OK	6.75	12.1	38.7	57.4	18.0	31.4	13.8	213.6	1278
908	OK	7.81	14.2	44.2	56.6	18.2	32.2	13.1	222.3	1217
909	OK	7.22	13.4	42.1	58.3	18.5	31.8	12.8	221.9	NP
910	OK	7.47	13.5	42.8	57.3	18.0	31.5	14.1	259.3	1491

Male, Group XI 30/0 mg/kg (Recovery) Day 29

Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
1101	OK	6.98	13.0	42.0	60.2	18.7	31.1	13.7	366.7	1410
1102	OK	6.80	13.3	41.1	60.5	19.5	32.2	14.3	396.5	1156
1103	OK	7.22	13.0	40.5	56.0	18.0	32.2	12.9	285.1	1179
1104	OK	6.52	12.8	40.7	62.4	19.6	31.4	14.6	406.3	963
1105	OK	6.68	12.4	39.4	59.0	18.6	31.5	15.7	422.5	NP
1106	OK	6.22	12.8	39.4	63.4	20.7	32.6	11.9	241.4	1278
1107	OK	6.67	12.3	37.7	56.5	18.4	32.6	13.5	369.9	1264
1108	OK	7.00	13.1	40.9	58.4	18.7	31.9	12.8	330.6	1391
1109	OK	6.28	12.3	39.6	63.1	19.5	31.0	19.3	563.7	NP
1110	OK	7.15	12.8	40.3	56.3	17.9	31.8	13.0	315.5	1015

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
101	16.73	2.54	13.11	0.42	0.34	0.06	0.26
102	12.13	1.03	10.69	0.22	0.05	0.05	0.09
103	17.69	1.59	15.23	0.28	0.31	0.08	0.21
104	10.15	1.22	8.63	0.15	0.06	0.03	0.06
105	6.35	0.45	5.65	0.12	0.06	0.02	0.05
106	10.92	1.27	9.16	0.20	0.12	0.06	0.11
107	NP	NP	NP	NP	NP	NP	NP
108	11.56	1.61	9.14	0.28	0.28	0.06	0.19
109	14.79	1.86	12.13	0.32	0.16	0.07	0.24
110	12.06	1.58	9.83	0.28	0.16	0.05	0.15

Male,	Group	III	0.3	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
301	12.65	1.84	10.21	0.19	0.16	0.08	0.17
302	12.13	1.78	9.90	0.26	0.05	0.02	0.12
303	15.31	1.87	12.73	0.41	0.12	0.05	0.13
304	16.29	1.14	14.70	0.17	0.11	0.05	0.13
305	11.09	1.30	9.29	0.24	0.03	0.10	0.13
306	8.30	0.67	7.33	0.11	0.08	0.03	0.07
307	7.40	1.01	6.10	0.12	0.06	0.04	0.07
308	11.29	2.14	8.65	0.29	0.07	0.06	0.09
309	10.11	1.04	8.64	0.20	0.10	0.02	0.11
310	9.52	1.04	8.07	0.21	0.06	0.03	0.11

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
501	17.11	1.54	14.87	0.37	0.08	0.12	0.13
502	14.81	2.13	12.15	0.24	0.08	0.08	0.14
503	10.66	0.95	9.24	0.28	0.07	0.04	0.10
504	9.63	0.99	8.26	0.20	0.02	0.03	0.13
505	12.87	1.29	11.07	0.24	0.05	0.06	0.14
506	11.28	1.42	9.39	0.11	0.13	0.13	0.10
507	14.91	1.38	13.15	0.14	0.06	0.05	0.11
508	16.44	1.28	14.54	0.31	0.09	0.05	0.16
509	9.61	1.18	8.04	0.20	0.09	0.02	0.08
510	15.45	3.33	11.14	0.52	0.18	0.07	0.21

Male,	Group	VII	10	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
701	16.43	1.44	14.29	0.26	0.16	0.08	0.20
702	15.57	1.66	13.11	0.34	0.11	0.10	0.24
703	15.38	1.85	13.38	0.00	0.15	0.00	0.00
704	13.51	0.84	12.30	0.19	0.04	0.04	0.11
705	12.35	1.70	9.95	0.34	0.12	0.08	0.16
706	14.85	2.43	11.64	0.38	0.29	0.03	0.09
707	21.39	2.30	17.99	0.62	0.10	0.10	0.28
708	15.73	1.03	13.84	0.39	0.05	0.12	0.29
709	19.09	1.25	16.99	0.26	0.13	0.11	0.34
710	18.32	2.13	15.20	0.47	0.11	0.07	0.33

Individual Animal Clinical Pathology Data

Male,	Group	IX	30	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
901	13.64	1.76	11.35	0.32	0.02	0.07	0.12
902	18.92	0.76	17.59	0.57	0.00	0.00	0.00
903	17.38	2.24	14.57	0.28	0.12	0.05	0.12
904	15.26	1.58	12.86	0.32	0.16	0.05	0.29
905	13.29	1.15	11.61	0.22	0.08	0.06	0.17
906	18.04	2.60	14.51	0.35	0.25	0.08	0.26
907	18.41	1.54	16.05	0.24	0.07	0.10	0.41
908	22.08	2.53	18.42	0.51	0.15	0.13	0.34
909	19.68	1.67	16.97	0.57	0.11	0.11	0.25
910	13.97	2.10	11.35	0.16	0.12	0.05	0.19

Male,	Group	XI	30/0	mg/kg	(Recovery)	Day	29
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
1101	13.64	1.09	12.14	0.27	0.14	0.00	0.00
1102	10.03	1.31	8.31	0.23	0.06	0.03	0.09
1103	15.43	0.93	13.41	0.29	0.17	0.07	0.56
1104	11.94	1.68	9.78	0.26	0.04	0.03	0.14
1105	11.44	2.30	8.74	0.17	0.09	0.05	0.08
1106	18.93	1.38	16.78	0.31	0.09	0.12	0.26
1107	23.15	1.89	19.98	0.53	0.21	0.16	0.39
1108	14.53	1.64	12.20	0.42	0.10	0.05	0.12
1109	8.10	0.99	6.71	0.25	0.03	0.04	0.09
1110	11.89	1.37	10.02	0.21	0.02	0.07	0.20

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
101	-	-	-	Trace	-	Few	Mod	-	-	-
102	Trace	-	Trace	Trace	Few	Trace	Trace	-	-	-
103	-	-	-	Trace	Trace	Few	Few	-	-	-
104	Trace	-	Trace	Trace	-	-	Trace	-	-	-
105	Few	-	Few	-	-	-	-	-	-	-
106	-	-	-	Trace	-	Mod	Few	-	-	-
107	CLOT	NP	NP	NP	NP	NP	NP	NP	NP	NP
108	-	-	-	-	-	-	-	-	-	-
109	-	-	-	-	-	Mod	Mod	-	-	-
110	-	-	-	-	-	-	-	-	-	-

Male,	Group	III	0.3	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
301	Trace	-	Trace	-	Few	-	-	-	-	-
302	-	-	-	-	-	-	-	-	-	-
303	-	-	-	-	-	-	-	-	-	-
304	Trace	-	Trace	Trace	-	-	Trace	-	-	-
305	-	-	-	-	-	-	-	-	-	-
306	-	-	-	-	-	-	-	-	-	-
307	-	-	-	-	Few	-	-	-	-	-
308	-	-	-	-	-	-	-	-	-	-
309	Few	-	Few	Trace	-	Few	Few	-	-	-
310	Trace	-	Trace	Trace	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
501	Trace	-	Trace	-	Few	Few	Trace	-	-	-
502	Trace	-	Trace	Trace	-	-	-	-	-	-
503	Trace	-	Trace	-	Mod	-	Trace	-	-	-
504	Trace	-	Trace	-	-	-	-	-	-	-
505	Trace	-	Trace	Trace	Mod	Trace	Trace	-	-	-
506	Trace	-	Trace	-	Trace	-	Trace	-	-	-
507	-	-	-	-	-	-	-	-	-	-
508	Trace	-	Trace	-	Few	-	-	-	-	-
509	Trace	-	Trace	Trace	Few	-	Few	-	-	-
510	-	-	-	Trace	-	-	-	-	-	-

Male,	Group	VII	10	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
701	Trace	-	Trace	Trace	Mod	-	Few	-	-	-
702	Trace	-	Trace	Few	Mod	-	Trace	-	-	-
703	Trace	-	Trace	Trace	Many	-	Trace	-	-	-
704	Trace	-	Trace	Trace	Mod	-	Trace	-	-	-
705	Trace	-	Trace	-	Many	-	-	-	-	-
706	Trace	-	Trace	Few	Few	-	Few	-	-	-
707	Trace	-	Trace	Trace	Few	-	-	-	-	-
708	Trace	-	Trace	-	Trace	-	-	-	-	-
709	Trace	-	Trace	Trace	Few	-	Few	-	-	-
710	Trace	-	Trace	Trace	Few	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	IX	30	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
901	Trace	-	Trace	Few	Mod	-	Trace	-	-	-
902	Trace	-	Trace	Trace	Trace	-	Trace	-	-	-
903	Trace	-	Trace	Trace	Many	-	Trace	-	-	-
904	Trace	-	Trace	-	-	-	-	-	-	-
905	Trace	-	Trace	Trace	Few	-	Trace	-	-	-
906	-	-	-	-	-	-	-	-	-	
907	Trace	-	Trace	Trace	Few	-	Few	-	-	-
908	Trace	Trace	Trace	Trace	Trace	-	-	-	-	-
909	-	-	-	Trace	Mod	-	-	-	-	-
910	Trace	Trace	Trace	Few	Few	-	Few	-	-	-

Male,	Group	XI	30/0	mg/kg	(Recovery)	Day	29			
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
1101	Trace	-	Trace	Mod	Few	Trace	Few	-	-	-
1102	Few	-	Few	Few	Mod	-	Trace	-	-	-
1103	Trace	-	Trace	Few	Mod	Trace	Few	-	-	-
1104	Few	-	Few	Mod	Mod	-	Trace	-	-	-
1105	Few	-	Few	Mod	Many	-	Few	-	-	-
1106	Trace	-	Trace	Few	Few	-	Few	-	-	-
1107	Trace	-	Trace	Few	Few	-	Few	-	-	-
1108	Trace	Trace	Trace	Few	Few	-	Trace	-	-	-
1109	Few	Trace	Few	Mod	Many	-	Few	-	-	-
1110	Trace	Trace	Trace	Few	Mod	Few	Few	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
101	-	-	-	-	-	Decr	-	-
102	-	-	-	-	-	-	-	-
103	-	-	-	-	-	Decr	-	-
104	-	-	-	-	-	-	-	-
105	-	-	-	-	-	-	-	-
106	-	-	-	-	-	-	-	-
107	CLOT	NP	NP	NP	NP	NP	NP	NP
108	-	-	-	-	-	Decr	-	-
109	-	-	-	-	-	-	-	-
110	-	-	-	-	-	-	-	-

Male,	Group	III	0.3	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
301	-	-	-	-	-	-	-	-
302	-	-	-	-	-	-	-	-
303	-	-	-	-	-	-	-	-
304	-	-	-	-	-	-	-	-
305	-	-	-	-	-	-	-	-
306	-	-	-	-	-	-	-	-
307	-	-	-	-	-	-	-	-
308	-	-	-	-	-	-	-	-
309	-	-	-	-	-	-	-	-
310	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
501	-	-	-	-	-	Adeq	-	-
502	-	-	-	-	-	-	-	-
503	-	-	-	-	-	-	-	-
504	-	-	-	-	-	-	-	-
505	-	-	-	-	-	Adeq	-	-
506	-	-	-	-	-	-	-	-
507	-	-	-	-	-	-	-	-
508	-	-	-	-	-	Adeq	-	-
509	-	-	-	-	-	-	-	-
510	-	-	-	-	-	Adeq	-	-

Male,	Group	VII	10	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
701	-	-	-	-	-	-	-	-
702	-	-	-	-	-	-	-	-
703	-	-	-	-	-	Decr	-	-
704	-	-	-	-	-	-	-	-
705	-	-	-	-	-	Decr	-	-
706	-	-	-	-	-	-	-	-
707	-	-	-	-	-	Adeq	-	-
708	-	-	-	-	-	-	-	-
709	-	-	-	-	-	-	-	-
710	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	IX	30	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
901	-	-	-	-	-	Adeq	-	-
902	-	-	-	-	-	-	-	-
903	-	-	-	-	-	-	-	-
904	-	-	-	-	-	Decr	-	-
905	-	-	-	-	-	-	-	-
906	-	-	-	-	-	-	-	-
907	-	-	-	-	-	-	-	-
908	-	-	-	-	-	-	-	-
909	-	-	-	-	-	Adeq	-	-
910	-	-	-	-	-	-	-	-

Male,	Group	XI	30/0	mg/kg	(Recovery)	Day	29	
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
1101	-	-	-	-	-	-	-	-
1102	-	-	-	-	-	-	-	-
1103	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	Adeq	-	-
1106	-	-	-	-	-	-	-	-
1107	-	-	-	-	-	-	-	-
1108	-	-	-	-	-	-	-	-
1109	-	-	-	-	-	Adeq	-	-
1110	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male, Group I 0 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
101	Small	None	None	95	57	6.4	3.4	3.0	29	66	213
102	None	None	None	67	92	6.1	3.3	2.8	27	40	32
103	None	None	None	70	65	6.4	3.4	3.0	25	45	104
104	None	None	None	58	50	5.9	3.3	2.6	22	36	60
105	None	None	None	46	36	5.9	3.3	2.6	19	27	109
106	None	None	None	56	59	6.1	3.2	2.9	21	35	218
107	None	None	None	91	88	6.4	3.5	2.9	31	60	50
108	None	None	None	55	66	6.2	3.3	2.9	23	32	251
109	None	None	None	57	94	5.9	3.1	2.8	22	35	283
110	None	None	None	43	69	6.1	3.3	2.8	19	24	46

Male, Group III 0.3 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
301	None	None	None	32	48	6.7	3.5	3.2	16	16	64
302	None	None	None	51	86	6.2	3.4	2.8	21	30	190
303	None	None	None	37	40	6.3	3.3	3.0	18	19	106
304	None	None	None	27	54	5.9	3.4	2.5	14	13	88
305	None	None	None	29	26	6.0	3.4	2.6	15	14	113
306	None	None	None	54	51	6.2	3.4	2.8	21	33	227
307	None	None	None	36	29	6.1	3.4	2.7	17	19	214
308	None	None	None	43	34	5.9	3.3	2.6	17	26	258
309	None	None	None	53	53	5.9	3.2	2.7	22	31	262
310	None	None	None	49	46	6.0	3.3	2.7	20	29	148

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29					
Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
501	None	None	None	64	99	6.4	3.6	2.8	26	38	221
502	None	None	None	43	54	6.7	3.7	3.0	22	21	70
503	None	None	None	34	44	6.0	3.5	2.5	15	19	107
504	None	None	None	44	47	5.8	3.5	2.3	19	25	155
505	None	None	None	48	51	6.4	3.6	2.8	21	27	128
506	Trace	None	None	42	43	6.5	3.6	2.9	18	24	50
507	Small	None	None	46	26	6.0	3.4	2.6	18	28	271
508	Trace	None	None	34	30	5.7	3.2	2.5	15	19	208
509	None	None	None	42	56	6.5	3.6	2.9	19	23	116
510	None	None	None	42	56	6.3	3.7	2.6	18	24	147

Male,	Group	VII	10	mg/kg	Day	29					
Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
701	Trace	None	None	55	47	5.9	3.5	2.4	20	35	174
702	Trace	None	None	48	47	6.5	3.8	2.7	18	30	354
703	Small	None	None	74	59	5.8	3.4	2.4	24	50	176
704	Small	None	None	52	25	5.7	3.5	2.2	19	33	158
705	None	None	None	53	42	6.0	3.5	2.5	19	34	302
706	Small	None	None	46	44	6.3	3.7	2.6	15	31	60
707	Small	None	None	55	81	6.8	4.0	2.8	21	34	88
708	Trace	None	None	41	32	6.3	3.8	2.5	16	25	119
709	Small	None	None	36	42	6.5	3.8	2.7	12	24	236
710	Small	None	None	59	40	5.6	3.5	2.1	20	39	182

Individual Animal Clinical Pathology Data

Male, Group IX 30 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
901	Small	None	None	46	55	5.8	3.7	2.1	16	30	436
902	None	None	None	70	48	6.3	3.7	2.6	26	44	736
903	Trace	None	None	50	55	6.4	3.8	2.6	18	32	370
904	Small	None	None	47	35	6.3	3.7	2.6	17	30	238
905	None	None	None	64	37	6.5	3.9	2.6	25	39	76
906	Trace	None	None	47	47	6.4	3.7	2.7	18	29	43
907	Small	None	None	64	26	6.0	3.8	2.2	22	42	331
908	Trace	None	None	47	42	5.8	3.6	2.2	16	31	38
909	Trace	None	None	53	44	5.9	3.7	2.2	16	37	287
910	None	None	None	55	62	6.7	3.9	2.8	20	35	124

Male, Group XI 30/0 mg/kg (Recovery) Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
1101	Small	None	None	88	45	6.8	3.9	2.9	29	59	71
1102	Trace	None	None	61	79	6.3	3.6	2.7	23	38	317
1103	None	None	None	122	57	7.0	3.9	3.1	35	87	90
1104	Trace	None	None	67	39	6.6	3.9	2.7	24	43	198
1105	None	None	None	84	64	7.0	4.2	2.8	28	56	68
1106	Small	None	None	64	25	6.4	3.7	2.7	25	39	54
1107	Small	None	None	36	35	6.3	3.6	2.7	15	21	89
1108	Trace	None	None	82	37	6.6	3.7	2.9	30	52	95
1109	None	None	None	62	44	5.4	3.2	2.2	22	40	245
1110	None	None	None	59	42	6.2	3.6	2.6	22	37	85

Appendix G
Individual Primary Humoral Immune Response Data

Individual Primary Humoral Immune Response Data

Animal Number	SLOPE	X	Log_2
Male, Group I - 0 mg/kg			
101	-0.8772	1648	10.687
102	-0.9165	872	9.768
103	-0.9442	5777	12.496
104	-1.0021	790	9.626
105	-0.9721	1355	10.404
106	-1.0214	2414	11.237
107	-1.0063	122	6.928
108	-1.0053	1586	10.631
109	-1.0377	394	8.622
110	-1.0022	1175	10.198
Male, Group III - 0.3 mg/kg			
301	-1.0141	1590	10.635
302	-0.9706	695	9.441
303	-1.0180	1237	10.273
304	-0.9477	1878	10.875
305	-1.0010	1854	10.856
306	-0.9884	1618	10.660
307	-0.9671	1605	10.648
308	-0.9972	1312	10.358
309	-0.9972	1095	10.097
310	-0.8896	914	9.836
Male, Group V - 1 mg/kg			
501	-0.9758	1307	10.352
502	-0.9001	2679	11.387
503	-0.9786	1559	10.606
504	-0.9388	111	6.794
505	-0.9980	915	9.838
506	-1.0325	1048	10.033
507	-0.9969	3228	11.656
508	-0.9742	791	9.628
509	-0.9732	227	7.826
510	-0.9843	1409	10.460

Individual Primary Humoral Immune Response Data

Animal Number	SLOPE	X	Log_2
Male, Group VII - 10 mg/kg			
701	-1.0199	788	9.622
702	-0.9756	956	9.901
703	-0.9847	201	7.650
704	-1.0187	855	9.740
705	-0.9605	2116	11.047
706	-0.9560	7340	12.842
707	-0.9836	494	8.948
708	-0.9532	86	6.426
709	-0.9399	3660	11.838
710	-0.9843	2287	11.159
Male, Group IX - 30 mg/kg			
901	-1.0014	1068	10.061
902	-1.0035	342	8.418
903	-1.0215	760	9.570
904	-0.9123	294	8.200
905	-1.0340	1788	10.804
906	-0.9742	2755	11.428
907	-0.9052	2078	11.021
908	-0.9060	457	8.836
909	-0.9504	1893	10.886
910	-1.0107	912	9.833
Male, Group XI - 30/0 mg/kg (Recovery)			
1101	-1.0040	543	9.085
1102	-0.9456	370	8.531
1103	-0.9969	392	8.615
1104	-0.9935	460	8.845
1105	-0.7713	1009	9.979
1106	-0.9712	2410	11.235
1107	-0.9856	314	8.295
1108	-0.9682	2447	11.257
1109	-0.9463	362	8.500
1110	-0.9972	1844	10.849

Appendix H
Individual Primary Humoral Immune Response Positive Control Data

Individual Primary Humoral Immune Response Positive Control Data

Animal Number	SLOPE	X	Log_2
Male, Group CIX - Saline			
C901	-1.0282	1215	10.247
C902	-1.0269	1400	10.451
C903	-0.9992	1249	10.287
C904	-1.0116	977	9.932
C905	-0.9398	820	9.679
C906	-0.9457	109	6.768
C907	-0.9708	554	9.114
C908	-0.9619	1255	10.293
C909	-0.9601	692	9.435
C910	-1.0013	328	8.358
Male, Group CXI - 20 mg/kg Cyclophosphamide			
C1101	-0.6474	4	2.000
C1102	-0.9816	14	3.807
C1103	-0.9912	18	4.170
C1104	-0.9556	12	3.585
C1105	-0.9067	23	4.524
C1106	-0.8857	26	4.700
C1107	-1.0035	55	5.781
C1108	-1.0031	15	3.907
C1109	-0.9962	14	3.807
C1110	-0.9898	26	4.700
Male, Pooled Samples - 20 mg/kg Cyclophosphamide			
	-0.9859	29	4.858
	-0.9832	12	3.625

Appendix I
Individual Animal Final Body and Organ Weights

Individual Animal Final Body and Organ Weights

Group: I Treatment: 0 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
101	455.90	2.163	0.4744	16.208	3.5552	749.33	1.143	0.2507	52.843	0.691	0.1516	31.946
102	441.60	1.995	0.4518	13.249	3.0002	664.11	0.761	0.1723	38.145	0.651	0.1474	32.632
103	445.00	2.122	0.4769	14.415	3.2393	679.31	0.976	0.2193	45.994	0.775	0.1742	36.522
104	427.00	1.959	0.4588	13.245	3.1019	676.11	0.771	0.1806	39.357	0.690	0.1616	35.222
105	390.80	2.072	0.5302	11.388	2.9140	549.61	0.806	0.2062	38.900	0.425	0.1088	20.512
106	404.70	1.949	0.4816	12.348	3.0511	633.56	0.669	0.1653	34.325	0.499	0.1233	25.603
107	387.90	2.004	0.5166	12.113	3.1227	604.44	0.617	0.1591	30.788	0.429	0.1106	21.407
108	405.90	1.948	0.4799	12.243	3.0163	628.49	1.008	0.2483	51.745	0.435	0.1072	22.331
109	457.80	2.038	0.4452	12.617	2.7560	619.09	0.944	0.2062	46.320	0.544	0.1188	26.693
110	414.60	1.873	0.4518	13.968	3.3690	745.76	0.744	0.1795	39.722	0.544	0.1312	29.044
Mean	423.12	2.012	0.4767	13.179	3.1126	654.98	0.844	0.1988	41.814	0.568	0.1335	28.191
S.D.	26.047	0.088	0.0280	1.397	0.2286	61.796	0.167	0.0330	7.2116	0.126	0.0238	5.7896

Group: III Treatment: 0.3 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
301	420.90	2.301	0.5467	15.614	3.7097	678.57	0.990	0.2352	43.025	0.704	0.1673	30.595
302	434.90	2.100	0.4829	16.174	3.7190	770.19	0.692	0.1591	32.952	0.828	0.1904	39.429
303	458.60	2.196	0.4788	15.448	3.3685	703.46	1.254	0.2734	57.104	0.504	0.1099	22.951
304	403.80	2.021	0.5005	14.184	3.5126	701.83	1.073	0.2657	53.093	0.652	0.1615	32.261
305	395.90	2.140	0.5405	12.639	3.1925	590.61	0.880	0.2223	41.121	0.619	0.1564	28.925
306	437.60	2.286	0.5224	14.947	3.4157	653.85	1.018	0.2326	44.532	0.689	0.1574	30.140
307	414.00	2.062	0.4981	13.090	3.1618	634.82	0.683	0.1650	33.123	0.421	0.1017	20.417
308	380.00	1.977	0.5203	11.256	2.9621	569.35	0.763	0.2008	38.594	0.457	0.1203	23.116
309	448.60	2.009	0.4478	15.946	3.5546	793.73	0.582	0.1297	28.970	0.577	0.1286	28.721
310	403.10	2.019	0.5009	14.488	3.5941	717.58	0.781	0.1937	38.683	0.587	0.1456	29.074
Mean	419.74	2.111	0.5039	14.379	3.4191	681.40	0.872	0.2078	41.120	0.604	0.1439	28.563
S.D.	24.955	0.117	0.0299	1.604	0.2497	71.841	0.209	0.0469	8.8488	0.123	0.0281	5.4395

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: V Treatment: 1 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
501	419.60	2.036	0.4852	23.052	5.4938	1132.2	0.725	0.1728	35.609	0.427	0.1018	20.972
502	395.30	2.090	0.5287	16.936	4.2843	810.33	0.762	0.1928	36.459	0.561	0.1419	26.842
503	439.20	2.031	0.4624	16.885	3.8445	831.36	0.907	0.2065	44.658	0.634	0.1444	31.216
504	441.30	2.108	0.4777	16.810	3.8092	797.44	1.004	0.2275	47.628	0.745	0.1688	35.342
505	364.70	2.086	0.5720	14.998	4.1124	718.98	0.673	0.1845	32.263	0.410	0.1124	19.655
506	408.80	1.987	0.4861	15.668	3.8327	788.53	0.836	0.2045	42.073	0.569	0.1392	28.636
507	369.90	2.096	0.5666	14.125	3.8186	673.90	0.660	0.1784	31.489	0.521	0.1408	24.857
508	406.10	2.093	0.5154	15.830	3.8981	756.33	0.938	0.2310	44.816	0.691	0.1702	33.015
509	476.20	2.307	0.4845	21.644	4.5451	938.19	1.085	0.2278	47.031	0.633	0.1329	27.438
510	379.20	2.028	0.5348	16.321	4.3041	804.78	0.758	0.1999	37.377	0.396	0.1044	19.527
Mean	410.03	2.086	0.5113	17.227	4.1943	825.21	0.835	0.2026	39.940	0.559	0.1357	26.750
S.D.	35.195	0.087	0.0383	2.860	0.5238	128.55	0.144	0.0210	6.0349	0.121	0.0238	5.5431

Group: VII Treatment: 10 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
701	354.30	1.933	0.5456	20.606	5.8160	1066.0	0.776	0.2190	40.145	0.679	0.1916	35.127
702	393.60	1.826	0.4639	22.561	5.7320	1235.5	0.760	0.1931	41.621	0.547	0.1390	29.956
703	382.60	2.053	0.5366	21.889	5.7211	1066.2	0.750	0.1960	36.532	0.674	0.1762	32.830
704	355.70	1.910	0.5370	17.564	4.9379	919.58	0.927	0.2606	48.534	0.420	0.1181	21.990
705	317.70	1.965	0.6185	16.749	5.2720	852.37	0.652	0.2052	33.181	0.319	0.1004	16.234
706	409.10	2.285	0.5585	25.831	6.3141	1130.5	0.767	0.1875	33.567	0.569	0.1391	24.902
707	421.10	2.029	0.4818	23.567	5.5965	1161.5	0.912	0.2166	44.948	0.717	0.1703	35.338
708	347.60	1.949	0.5607	19.401	5.5814	995.43	0.625	0.1798	32.068	0.528	0.1519	27.091
709	409.00	2.057	0.5029	23.440	5.7311	1139.5	0.898	0.2196	43.656	0.734	0.1795	35.683
710	378.80	1.983	0.5235	23.086	6.0945	1164.2	1.017	0.2685	51.286	0.626	0.1653	31.568
Mean	376.95	1.999	0.5329	21.469	5.6797	1073.1	0.808	0.2146	40.554	0.581	0.1531	29.072
S.D.	32.760	0.123	0.0438	2.864	0.3849	119.55	0.126	0.0296	6.6706	0.134	0.0290	6.4726

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: IX Treatment: 30 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
901	272.60	1.814	0.6654	15.544	5.7021	856.89	0.498	0.1827	27.453	0.299	0.1097	16.483
902	294.00	1.946	0.6619	15.920	5.4150	818.09	0.633	0.2153	32.528	0.668	0.2272	34.327
903	394.10	2.086	0.5293	22.466	5.7006	1077.0	0.779	0.1977	37.344	0.765	0.1941	36.673
904	284.00	2.135	0.7518	15.315	5.3926	717.33	0.673	0.2370	31.522	0.191	0.0673	8.9461
905	329.20	1.961	0.5957	18.034	5.4781	919.63	0.673	0.2044	34.319	0.563	0.1710	28.710
906	303.40	2.043	0.6734	18.366	6.0534	898.97	0.713	0.2350	34.900	0.582	0.1918	28.488
907	334.00	1.979	0.5925	23.114	6.9204	1168.0	0.762	0.2281	38.504	0.487	0.1458	24.608
908	303.80	1.908	0.6280	18.002	5.9256	943.50	0.734	0.2416	38.470	0.372	0.1224	19.497
909	335.00	2.144	0.6400	21.838	6.5188	1018.6	0.691	0.2063	32.229	0.487	0.1454	22.715
910	294.10	1.904	0.6474	18.242	6.2027	958.09	0.586	0.1993	30.777	0.453	0.1540	23.792
Mean	314.42	1.992	0.6385	18.684	5.9309	937.60	0.674	0.2147	33.805	0.487	0.1529	24.424
S.D.	35.139	0.108	0.0590	2.866	0.5033	129.37	0.085	0.0198	3.6004	0.171	0.0463	8.2546

Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
1101	329.40	1.808	0.5489	17.005	5.1624	940.54	0.596	0.1809	32.965	0.607	0.1843	33.573
1102	343.20	1.964	0.5723	17.783	5.1815	905.45	0.782	0.2279	39.817	0.619	0.1804	31.517
1103	344.00	1.993	0.5794	16.745	4.8677	840.19	0.722	0.2099	36.227	0.739	0.2148	37.080
1104	393.00	2.056	0.5232	19.117	4.8644	929.82	1.076	0.2738	52.335	0.834	0.2122	40.564
1105	336.60	1.999	0.5939	17.024	5.0576	851.63	0.665	0.1976	33.267	0.571	0.1696	28.564
1106	386.50	1.914	0.4952	17.552	4.5413	917.03	1.013	0.2621	52.926	0.776	0.2008	40.543
1107	312.50	1.782	0.5702	16.575	5.3040	930.13	0.841	0.2691	47.194	0.534	0.1709	29.966
1108	283.60	1.641	0.5786	11.859	4.1816	722.67	0.624	0.2200	38.026	0.483	0.1703	29.433
1109	287.60	1.969	0.6846	13.520	4.7010	686.64	0.548	0.1905	27.831	0.624	0.2170	31.691
1110	321.50	2.003	0.6230	14.881	4.6286	742.94	0.936	0.2911	46.730	0.606	0.1885	30.255
Mean	333.79	1.913	0.5769	16.206	4.8490	846.70	0.780	0.2323	40.732	0.639	0.1909	33.319
S.D.	36.149	0.129	0.0521	2.170	0.3449	95.980	0.182	0.0390	8.6409	0.110	0.0190	4.5108

FBW - Final Body Weight

Appendix J
Individual Animal Pathology Data

INDIVIDUAL ANIMAL PATHOLOGY DATA

KEY TO APPENDIX

LESION GRADING:

Histopathology changes are described according to their morphologic character, distribution and severity. The distribution (extent of tissue involvement) is indicated, where appropriate, by modifiers such as focal, multifocal, diffuse, unilateral, bilateral, etc. A severity score, if appropriate, is also assigned as follows:

MINIMAL: The amount of change present barely exceeds that which is considered to be within normal limits.

MILD: In general, the lesion is easily identified but of limited severity. The lesion probably does not produce any functional impairment.

MODERATE: The lesion is prominent but there is significant potential for increased severity. Limited tissue or organ dysfunction is possible.

SEVERE: The degree of change is either as complete as considered possible or great enough in intensity or extent to expect significant tissue or organ dysfunction.

COMMENT:

Grades minimal through severe represent progressive involvement/severity along a continuum with minimal lesions being the least severe and severe lesions being the most severe. While the grades refer to the morphologic characteristics of lesions, they also indicate their relative biologic significance.

Gross observations listing multiple masses for a tissue are distinguished with letters (i.e., a, b, c, d, etc.).

Individual Animal Pathology Data

Dose Group: I Treatment: 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
101	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Animal Ref	Microscopic & Macroscopic Findings
102	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

102 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: I Treatment: 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
102	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
103	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. FATTY CHANGE, MEDIAN CLEFT, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN. POPLITEAL LYMPH NODE : NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
104	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

104 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: I Treatment: 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
104	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

105 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

106 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

106 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: I Treatment: 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
106	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

107 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
BONE MARROW :
FIBROSIS, FOCAL, minimal, (femur).
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM

Individual Animal Pathology Data

Dose Group: I Treatment: 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
108	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
BRAIN :
PIGMENT, FOCAL, minimal, hemosiderin (cerebellum).
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT,
STERNUM, BONE MARROW

Animal Ref	Microscopic & Macroscopic Findings
109	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
FATTY CHANGE, MEDIAN CLEFT, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

109 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: I Treatment: 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
109	Continued from previous page
	Histopathology :
	POPLITEAL LYMPH NODE :
	NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed :
	SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
110	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	POPLITEAL LYMPH NODE :
	NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed :
	SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Dose Group: III Treatment: 0.3 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
301	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
302	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.

302 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: III Treatment: 0.3 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
302	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN
303	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
304	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

304 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: III Treatment: 0.3 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
304	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
305	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with
	cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
306	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

306 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: III Treatment: 0.3 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
306	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
307	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
308	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Dose Group: III Treatment: 0.3 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
308	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
309	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with
	cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
310	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

310 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: III Treatment: 0.3 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
310	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN

Individual Animal Pathology Data

Dose Group: V Treatment: 1 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
501	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
502	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. SPLEEN : HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.

Individual Animal Pathology Data

Dose Group: V Treatment: 1 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
503	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology : No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology : LIVER : INFLAMMATION, SUBACUTE/CHRONIC, mild. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN. No Microscopic Abnormality Observed : SPLEEN
504	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology : No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology : LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.

504 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: V Treatment: 1 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
504	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN
505	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
506	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

506 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: V Treatment: 1 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
506	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
507	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
508	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

508 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: V Treatment: 1 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
508	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
509	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
510	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Dose Group: V Treatment: 1 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
510	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN

Individual Animal Pathology Data

Dose Group: VII Treatment: 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
701	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
702	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.

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Individual Animal Pathology Data

Dose Group: VII Treatment: 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
702	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN
703	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERPLASIA, BILE DUCT, FOCAL, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
704	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Dose Group: VII Treatment: 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
704	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
705	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	DISCOLORATION, TAN, LEFT, LINEAR <3MM .
	No Macroscopic Abnormality Observed :
	SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN

Individual Animal Pathology Data

Dose Group: VII Treatment: 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
706	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
707	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. NECROSIS, FOCAL, minimal, coagulative. MINERALIZATION, BILE DUCT, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH : SACRIFICE BY DESIGN.

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Individual Animal Pathology Data

Dose Group: VII Treatment: 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
707	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN
708	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN
709	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Dose Group: VII Treatment: 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
709	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, mild.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN
710	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.

Individual Animal Pathology Data

Dose Group: IX Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
901	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. INFLAMMATION, SUBACUTE/CHRONIC, minimal. MESENTERIC LYMPH NODE : DEPLETION/ATROPHY, LYMPHOID, minimal, (inner cortex, outer cortex, and follicles). CAUSE OF DEATH : SACRIFICE BY DESIGN. POPLITEAL LYMPH NODE : NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
902	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal.

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Individual Animal Pathology Data

Dose Group: IX Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
902	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

903 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

Individual Animal Pathology Data

Dose Group: IX Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
904	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, mild. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, FOCAL, minimal, coagulative, subcapsular. CAUSE OF DEATH : SACRIFICE BY DESIGN. POPLITEAL LYMPH NODE : NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
905	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	LIVER : DISCOLORATION, TAN, MOTTLED.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

905 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: IX Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
905	Continued from previous page

Histopathology :

LIVER :
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

906 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

Individual Animal Pathology Data

Dose Group: IX Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
907	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE DISCOLORATION, PALE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, FOCAL, minimal, coagulative, subcapsular. INFLAMMATION, SUBACUTE/CHRONIC, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE
908	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal.

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Individual Animal Pathology Data

Dose Group: IX Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
908	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

909 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
NECROSIS, FOCAL, minimal, coagulative.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

Individual Animal Pathology Data

Dose Group: 1X Treatment: 30 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
910	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1101	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	LIVER : DISCOLORATION, TAN, MOTTLED, LEFT.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. SPLEEN : HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal. BONE MARROW : FIBROSIS, FOCAL, minimal, (femur). CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
1102	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

1102 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1102	Continued from previous page

Histopathology :

LIVER :
MINERALIZATION, BILE DUCT, moderate, with fibrosis.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

1103 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1104	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

1105	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.

1105 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1105	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

1106 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
POPLITEAL LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1107	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. INFLAMMATION, SUBACUTE/CHRONIC, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE
1108	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
1108	Continued on the next page ....

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1108	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE
1109	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. INFLAMMATION, SUBACUTE/CHRONIC, minimal. FIBROSIS, FOCAL, minimal, subcapsular. SPLEEN : HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, mild. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE
1110	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

1110 Continued on the next page ....

Individual Animal Pathology Data

Dose Group: XI Treatment: 30/0 mg/kg (Recovery) Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
1110	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
NECROSIS, FOCAL, minimal, coagulative.
SPLEEN :
HEMATOPOIESIS, EXTRAMEDULLARY, INCREASED, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, POPLITEAL LYMPH NODE

Appendix K
Individual Total Cell Counts

INDIVIDUAL TOTAL CELL COUNTS

EXPLANATORY NOTES

NOTES:

$$\text{Organ Weight as Percent of Body Weight} = \frac{\text{Organ Weight (g)}}{\text{Final Body Weight (g)}} \times 100$$

$$\text{Total Number of Organ Cells } (\times 10^8) = \frac{\text{Organ Weight (g)}}{\text{Half Organ Weight (g)}} \times \text{Organ Cell Suspension Volume (mL)} \times \text{Number of Cells in Half Organ } (\times 10^6 \text{ cells/mL}) \div 100$$

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells ($x10^8$)
Male, Group I - 0 mg/kg							
101	455.90	1.143	0.2507	0.589	7.8	71.50	10.82
102	441.60	0.761	0.1723	0.379	7.0	27.50	3.87
103	445.00	0.976	0.2193	0.511	7.0	53.90	7.21
104	427.00	0.771	0.1806	0.411	7.2	58.30	7.87
105	390.80	0.806	0.2062	0.439	6.5	22.00	2.63
106	404.70	0.669	0.1653	0.346	6.3	26.40	3.22
107	387.90	0.617	0.1591	0.303	7.2	35.20	5.16
108	405.90	1.008	0.2483	0.506	7.2	22.00	3.16
109	457.80	0.944	0.2062	0.499	6.5	45.10	5.55
110	414.60	0.744	0.1795	0.370	6.5	53.90	7.04
Male, Group III - 0.3 mg/kg							
301	420.90	0.990	0.2352	0.485	7.0	66.00	9.43
302	434.90	0.692	0.1591	0.365	7.0	26.40	3.50
303	458.60	1.254	0.2734	0.645	7.8	71.50	10.84
304	403.80	1.073	0.2657	0.556	7.4	66.00	9.43
305	395.90	0.880	0.2223	0.468	7.0	27.50	3.62
306	437.60	1.018	0.2326	0.514	7.0	35.20	4.88
307	414.00	0.683	0.1650	0.349	7.0	42.90	5.88
308	380.00	0.763	0.2008	0.384	7.0	35.20	4.90
309	448.60	0.582	0.1297	0.281	6.8	36.30	5.11
310	403.10	0.781	0.1937	0.380	6.5	35.20	4.70

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells (x10^8)
Male, Group V - 1 mg/kg							
501	419.60	0.725	0.1728	0.366	9.9	38.50	7.55
502	395.30	0.762	0.1928	0.364	7.5	42.90	6.74
503	439.20	0.907	0.2065	0.459	7.5	18.70	2.77
504	441.30	1.004	0.2275	0.545	7.2	105.60	14.01
505	364.70	0.673	0.1845	0.366	7.0	22.00	2.83
506	408.80	0.836	0.2045	0.416	6.5	30.80	4.02
507	369.90	0.660	0.1784	0.301	7.0	52.80	8.10
508	406.10	0.938	0.2310	0.497	7.2	34.10	4.63
509	476.20	1.085	0.2278	0.521	7.5	44.00	6.87
510	379.20	0.758	0.1999	0.375	7.0	49.50	7.00
Male, Group VII - 10 mg/kg							
701	354.30	0.776	0.2190	0.397	8.0	52.80	8.26
702	393.60	0.760	0.1931	0.399	7.0	16.50	2.20
703	382.60	0.750	0.1960	0.430	6.5	79.20	8.98
704	355.70	0.927	0.2606	0.453	6.8	36.30	5.05
705	317.70	0.652	0.2052	0.374	7.0	45.10	5.50
706	409.10	0.767	0.1875	0.368	7.8	48.40	7.87
707	421.10	0.912	0.2166	0.455	6.9	39.60	5.48
708	347.60	0.625	0.1798	0.304	7.0	50.60	7.28
709	409.00	0.898	0.2196	0.448	6.5	33.00	4.30
710	378.80	1.017	0.2685	0.530	7.4	52.80	7.50

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells (x10^8)
Male, Group IX - 30 mg/kg							
901	272.60	0.498	0.1827	0.293	10.0	25.30	4.30
902	294.00	0.633	0.2153	0.297	10.2	12.10	2.63
903	394.10	0.779	0.1977	0.367	7.5	46.20	7.35
904	284.00	0.673	0.2370	0.340	6.8	26.40	3.55
905	329.20	0.673	0.2044	0.368	7.3	36.30	4.85
906	303.40	0.713	0.2350	0.334	7.0	23.10	3.45
907	334.00	0.762	0.2281	0.416	6.3	33.00	3.81
908	303.80	0.734	0.2416	0.388	6.5	70.40	8.66
909	335.00	0.691	0.2063	0.346	7.0	20.90	2.92
910	294.10	0.586	0.1993	0.330	6.5	49.50	5.71
Male, Group XI - 30/0 mg/kg (Recovery)							
1101	329.40	0.596	0.1809	0.317	7.1	58.30	7.78
1102	343.20	0.782	0.2279	0.392	6.5	29.70	3.85
1103	344.00	0.722	0.2099	0.357	6.8	33.00	4.54
1104	393.00	1.076	0.2738	0.529	6.8	66.00	9.13
1105	336.60	0.665	0.1976	0.353	7.0	36.30	4.79
1106	386.50	1.013	0.2621	0.552	7.0	58.30	7.49
1107	312.50	0.841	0.2691	0.436	6.5	48.40	6.07
1108	283.60	0.624	0.2200	0.360	6.5	61.60	6.94
1109	287.60	0.548	0.1905	0.248	7.2	15.40	2.45
1110	321.50	0.936	0.2911	0.470	6.5	37.40	4.84

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group I - 0 mg/kg						
101	0.691	0.1516	0.343	7.5	77.00	11.63
102	0.651	0.1474	0.331	7.5	112.75	16.63
103	0.775	0.1742	0.388	7.5	121.00	18.13
104	0.690	0.1616	0.371	7.0	111.10	14.46
105	0.425	0.1088	0.219	6.5	65.45	8.26
106	0.499	0.1233	0.266	7.0	72.05	9.46
107	0.429	0.1106	0.197	7.2	85.25	13.37
108	0.435	0.1072	0.223	7.5	78.10	11.43
109	0.544	0.1188	0.269	7.2	80.30	11.69
110	0.544	0.1312	0.232	7.5	47.30	8.32
Male, Group III - 0.3 mg/kg						
301	0.704	0.1673	0.367	6.5	18.70	2.33
302	0.828	0.1904	0.388	7.5	137.50	22.01
303	0.504	0.1099	0.266	7.5	68.75	9.77
304	0.652	0.1615	0.330	7.0	84.15	11.64
305	0.619	0.1564	0.293	7.0	116.60	17.24
306	0.689	0.1574	0.324	7.0	132.00	19.65
307	0.421	0.1017	0.225	6.8	72.05	9.17
308	0.457	0.1203	0.192	7.0	72.60	12.10
309	0.577	0.1286	0.238	7.0	78.10	13.25
310	0.587	0.1456	0.292	7.0	51.15	7.20

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group V - 1 mg/kg						
501	0.427	0.1018	0.237	6.6	67.10	7.98
502	0.561	0.1419	0.277	7.5	70.40	10.69
503	0.634	0.1444	0.307	7.8	135.85	21.88
504	0.745	0.1688	0.341	7.0	89.10	13.63
505	0.410	0.1124	0.199	7.0	59.40	8.57
506	0.569	0.1392	0.278	7.0	111.65	16.00
507	0.521	0.1408	0.264	7.0	108.90	15.04
508	0.691	0.1702	0.354	7.5	112.75	16.51
509	0.633	0.1329	0.291	7.4	84.70	13.63
510	0.396	0.1044	0.172	7.3	46.75	7.86
Male, Group VII - 10 mg/kg						
701	0.679	0.1916	0.341	7.7	123.20	18.89
702	0.547	0.1390	0.268	7.2	81.40	11.96
703	0.674	0.1762	0.353	7.5	107.25	15.36
704	0.420	0.1181	0.237	6.8	39.05	4.71
705	0.319	0.1004	0.143	7.5	49.50	8.28
706	0.569	0.1391	0.295	6.5	157.30	19.72
707	0.717	0.1703	0.303	6.8	145.20	23.36
708	0.528	0.1519	0.260	7.3	81.95	12.15
709	0.734	0.1795	0.366	7.0	119.35	16.75
710	0.626	0.1653	0.323	7.4	63.80	9.15

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells ($x10^8$)
Male, Group IX - 30 mg/kg						
901	0.299	0.1097	0.153	7.4	46.20	6.68
902	0.668	0.2272	0.333	7.5	110.50	16.62
903	0.765	0.1941	0.401	7.6	102.85	14.91
904	0.191	0.0673	0.116	6.8	21.45	2.40
905	0.563	0.1710	0.280	7.0	105.05	14.79
906	0.582	0.1918	0.269	7.5	80.30	13.03
907	0.487	0.1458	0.227	7.3	152.90	23.95
908	0.372	0.1224	0.167	7.0	39.05	6.09
909	0.487	0.1454	0.269	7.0	72.60	9.20
910	0.453	0.1540	0.254	7.0	72.05	8.99
Male, Group XI - 30/0 mg/kg (Recovery)						
1101	0.607	0.1843	0.307	7.4	127.60	18.67
1102	0.619	0.1804	0.330	7.5	112.20	15.78
1103	0.739	0.2148	0.378	7.0	148.50	20.32
1104	0.834	0.2122	0.365	7.5	177.65	30.44
1105	0.571	0.1696	0.296	7.3	121.00	17.04
1106	0.776	0.2008	0.428	7.3	169.40	22.42
1107	0.534	0.1709	0.268	7.3	130.35	18.96
1108	0.483	0.1703	0.238	7.0	66.00	9.38
1109	0.624	0.2170	0.315	7.0	92.95	12.89
1110	0.606	0.1885	0.320	7.3	63.80	8.82

Appendix L
Electron Microscopy Report from Experimental Pathology Laboratories, Inc.

EPL® Experimental Pathology Laboratories, Inc.

DUPONT/HASKELL LABORATORY

DUPONT STUDY NUMBER: 18317
WORK REQUEST NUMBER: 16160
SERVICE CODE: 1545

AMMONIUM PERFLUOROOCTANOATE: 28-DAY IMMUNOTOXICITY STUDY IN MALE RATS

ELECTRON MICROSCOPY

PATHOLOGY REPORT
EPL PROJECT NO. 129-077

Submitted to:

DuPont/Haskell Laboratory for Health
and Environmental Science
Stine Haskell Research Center
1090 Elkton Road
Newark, DE 19711

Submitted by:

Experimental Pathology Laboratories, Inc.
P.O. Box 12766
Research Triangle Park, NC 27709

October 25, 2006

EPL® Experimental Pathology Laboratories, Inc.

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EPL® Experimental Pathology Laboratories, Inc.

DuPont-18317

DUPONT/HASKELL LABORATORY

DUPONT STUDY NUMBER: 18317
WORK REQUEST NUMBER: 16160
SERVICE CODE: 1545

EPL PROJECT NO.: 129-077

AMMONIUM PERFLUOROOCTANOATE: 28-DAY IMMUNOTOXICITY STUDY IN MALE RATS

ELECTRON MICROSCOPY

PATHOLOGY SUMMARY

The in-life phase of this study was conducted at Haskell Laboratory for Health and Environmental Sciences, E.I. duPont de Nemours and Company, Newark, Delaware. The objective of this study is to evaluate the potential of ammonium perfluorooctanoate to suppress the primary humoral immune response to sheep red blood cells (SRBC) when administered by oral gavage to male rats for at least 28 days. The table below summarizes the experimental design:

Experimental Design

Group	Number/Group	Daily Dosage (mg/kg)[a]	Dose Solution Concentration (mg/mL)[b]
I	10	0 (Control)	0
III	10	0.3	0.03
V	10	1	0.1
VII	10	10	1
IX	10	30	3
XI	10	30 (Recovery)[c]	3

[a] Weight of test substance/kg of animal body weight.
[b] Solutions will be adjusted for purity (20%)
[c] The recovery group (XI) will be dosed with 30 mg/kg of test substance through test day 22. Following injection of SRBC on test day 23, group XI will be dosed with NANOpure® water, at a volume of 10 mL/kg of body weight, until sacrifice.

Electron microscopic evaluation of samples of liver from designated animals was added to clarify light microscopic histopathological findings in the liver. Samples of liver from two male

EPL® Experimental Pathology Laboratories, Inc.

rats in Group I (Control) and two male rats in Group IX (30 mg/kg) that were fixed in formalin were submitted for transmission electron microscopy. The samples that were processed and evaluated are listed in the following table:

TEM Number	Tissue	Animal ID	Group	TEM Negative Number (evaluated)
G06-399	Liver	105	I (Control)	06-1894 to 06-1896
G06-400	Liver	106	I (Control)	06-1897 to 06-1899
G06-401	Liver	905	IX (30 mg/kg)	06-1900 to 06-1902
G06-402	Liver	906	IX (30 mg/kg)	06-1903 to 06-1905

Samples, cut into small cubes, were preserved in formalin and shipped to Experimental Pathology Laboratories, Inc (EPL®), Research Triangle Park, NC. The samples were transferred to the Laboratory for Advanced Electron and Light Optical Methods (LAELOM) at the College of Veterinary Medicine, North Carolina State University, Raleigh, NC for further processing and examination by transmission electron microscopy.

The samples were washed in buffer, post-fixed in 1% osmium tetroxide in the phosphate buffer, dehydrated in an ethanolic series culminating in acetone, and infiltrated with Spurr epoxide resin. The resulting blocks were trimmed and semithin sections (approximately 0.5 µm thick) were cut, mounted on glass slides, and stained with 1% toluidine blue O in 1% sodium borate prior to being examined with a light microscope. The slides of semithin sections were sent to Experimental Pathology Laboratories for evaluation by the Pathologist, Dr. Henry Wall. When the slides were returned to the LAELOM, areas of interest for ultrathin sectioning were trimmed in the corresponding tissue blocks.

Ultrathin (80-90 nm thick) sections were cut from the selected trimmed blocks and placed on 200 mesh copper grids before being stained with uranyl acetate and lead citrate. For each sample, two survey photographs (final print magnification 5,600x) were taken. One higher magnification (final print magnification 22,400x) was taken of each sample to show more cellular detail.

RESULTS

TEM #G06-399 (Animal 105, Control, Liver, TEM Neg # 06-1894 to 06-1896)

Two low magnification images (06-1894 and 06-1895; 5,600X) depict portions of multiple hepatocytes. A few clear to moderately electron-lucent smooth-contoured lipid droplets are in the cytoplasm of most hepatocytes. The cytoplasm of all hepatocytes contain numerous well-formed mitochondria as the predominant cytoplasmic organelles. The higher magnification image (06-1896; 22,400X) shows greater detail of the hepatocytic mitochondria, lipid droplets, cisternae of rough endoplasmic reticulum, a few electron-dense membrane-bound peroxisomes, and electron dense clusters of cytoplasmic glycogen. No cell injury is apparent.

TEM #G06-400 (Animal 106, Control, Liver, TEM Neg # 06-1897 to 06-1899)

Both low magnification images (06-1897 and 06-1898; 5,600X) show multiple hepatocytes that have numerous mitochondria as their predominant cytoplasmic organelles. Aggregates of linearly arrayed rough endoplasmic reticulum are scattered in the cytoplasm of hepatocytes. The high magnification image (06-1899; 22,400X) shows greater detail of the several mitochondria, rough endoplasmic reticulum, and a few slightly electron-dense lysosomes. A few of the smaller diameter electron-dense bodies may be peroxisomes, however, their structure is not optically resolved to the extent that their identity as peroxisomes can be confirmed. Irregular profiles of translucent smooth endoplasmic reticulum are interspersed between other organelles in the cytoplasm. A portion of a well formed nucleus is at the lower right of the image. No cell injury is present.

TEM #G06-401 (Animal 905, Group IX/30mg/kg, Liver, TEM Neg # 06-1900 to 06-1902)

Both low magnification images (06-1900 and 06-1901; 5,600X) depict multiple hepatocytes with abundant densely arranged cytoplasmic mitochondria. Peroxisomes which appear as uniformly electron-dense bodies are prominent among the mitochondria. A few small clear smooth-contoured vacuoles are in most cells. These vacuoles are considered to be lipid vacuoles that lost their content during tissue processing. A few lysosomes are in some hepatocytes. Most lysosomes contain either lipid droplets or electron-dense residual bodies. In one image (06-1901) a cross section of a blood vessel contains electron-dense erythrocytes and shows the nucleus of an endothelial cell. The higher magnification image (06-1902;

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22,400X) shows more detail of clear lipid vacuoles, numerous mitochondria, a lipid-laden lysosome and a few electron-dense peroxisomes. The peroxisomes are along the right border of the image and in the upper left quadrant of the image.

TEM #G06-402 (Animal 906, Group IX/30mg/kg, Liver, TEM Neg # 06-1903 to 06-1905)

The low magnification images (06-1903 and 06-1904; 5,600X) show numerous mitochondria as the predominant organelles in the cytoplasm of adjacent hepatocytes. Several uniformly electron-dense peroxisomes are scattered in the cells but are somewhat difficult to discern in the low magnification images. The high magnification image (06-1905; 22,400X) shows the detail of several peroxisomes in hepatocytic cytoplasm at the periphery of the endothelium of a blood vessel along the left border of the image. The peroxisomes are generally smaller in diameter than the more numerous mitochondria in the image. The peroxisomes are lined by a single membrane and have relatively uniform electron-dense matrix in this high magnification image.

CONCLUSIONS

Compared to hepatocytes from the two control rats, the hepatocytes from the two rats that received ammonium perfluorooctanoate have more abundant peroxisomes in their cytoplasm.

Henry G. Wall

HENRY G.WALL, DVM, PhD
Diplomate, ACVP
Veterinary Pathologist

25 October 2006
Date

HGW/dc

EPL® Experimental Pathology Laboratories, Inc.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Ammonium Perfluorooctanoate: 28-Day Immunotoxicity Study in Male Rats

Client Study: DuPont-18317; Service Code 1545; Work Request 16160

EPL Project Coordinator: Dr. Henry Wall

EPL Project Number: 129-077

EPL Pathologist: Dr. Henry Wall

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Project Coordinator and Management are indicated below.

Area Inspected	Dates Inspection	Dates Reporting
EPL Project Sheets	May 30, 2006	May 30, 2006
Data Review	June 14, 2006	June 14, 2006
Draft Pathology Report	June 27, 2006	June 27, 2006
Final Pathology Report	October 25, 2006	October 25, 2006

Date reported to Study Director/Management: October 25, 2006

Date of last quarterly facility inspection: October 2006

Jane J. Hollingsworth
EPL Quality Assurance Unit

October 25, 2006
Date

5

Form No. 6-2 (October 23, 2006)

TRADE SECRET

Study Title

Ammonium Perfluorooctanoate: 28-Day Immunotoxicity Study in Male Mice

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.7800 (1998)

AUTHOR: Denise Hoban, B.A, MLT (ASCP)

STUDY COMPLETED ON: February 1, 2007

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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LABORATORY PROJECT ID: DuPont-18318

WORK REQUEST NUMBER: 16160

SERVICE CODE NUMBER: 1546

SPONSOR: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

PAGE RESERVED

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA FIFRA (40 CFR part 160) Good Laboratory Practice Standards, which are compatible with current OECD and MAFF (Japan) Good Laboratory Practices, except for the item documented below. The item listed does not impact the validity of the study.

A non-GLP characterization was performed prior to the initiation of this study. The accuracy of the composition at the concentrations documented in this report is considered sufficient for the purpose of this study and is based on the process chemistry provided by the sponsor. GLP characterization was performed concurrently during the course of the study.

Applicant / Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Director: Denise Hoban 01 Feb 2007
Denise Hoban, B.A, MLT (ASCP) Date
Staff Medical Technologist and Supervisor

Applicant / Sponsor: _____ _____
DuPont Representative Date

QUALITY ASSURANCE STATEMENT

Work Request Number: 16160
Study Code Number: 1546

Phase Audited	*Audit Dates*	*Date Reported to Study Director*	*Date Reported to Management*
Protocol:	October 17, 2005	October 17, 2005	October 17, 2005
Conduct:	November 11, 2005	November 11, 2005	November 11, 2005
	November 17, 2005	November 18, 2005	November 18, 2005
	May 30, 2006*	October 31, 2006*	November 2, 2006*
	June 14, 2006*	October 31, 2006*	November 2, 2006*
	June 27, 2006*	October 31, 2006*	November 2, 2006*
	July 24, 2006*	October 31, 2006*	November 2, 2006*
	October 25, 2006*	October 31, 2006*	November 2, 2006*
Report/Records:	February 2, 7, 2006	February 7, 2006	February 8, 2006
	August 18, 21-24, 2006	August 25, 2006	October 19, 2006
	November 28-29, 2006	November 29, 2006	January 8, 2007

* EPL QA Dates

Reported by: Joseph C Hamill 01-Feb-2007
Joseph C. Hamill
Quality Assurance Auditor
Date

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

Analytical Evaluation by: _____ 01-Feb-2007
Z. Amanda Shen, Ph.D. — Date
Research Chemist

Clinical Pathology Evaluation by: _____ 01-Feb-2007
Nancy E. Everds, D.V.M., Diplomate A.C.V.P. — Date
Principal Research Clinical Pathologist and Manager

Anatomic Pathology Evaluation by: _____ 01-Feb-2007
Greg P. Sykes, V.M.D., Diplomate A.C.V.P., A.C.L.A.M., A.B.T.® — Date
Veterinary Pathologist

Anatomic Pathology Evaluation Peer Review by: _____ 01-Feb-2007
Steven R. Frame, D.V.M., Ph.D., Diplomate A.C.V.P. — Date
Research Fellow and Manager

Reviewed and Approved by: _____ 01-FEB-2007
Scott E. Loveless, Ph.D. — Date
Research Manager and Director

Issued by Study Director: _____ 01Feb 2007
Denise Hoban, B.A, MLT (ASCP) — Date
Staff Medical Technologist and Supervisor

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STUDY INFORMATION

Substance Tested:	• Ammonium Perfluorooctanoate [APFO (linear)] • 3825-26-1 (CAS Number)
Haskell Number:	27308
Composition:	Ammonium Perfluoroctanoate Solution 19.5% in water
Purity:	19.5%
Physical Characteristics:	White to slightly opaque liquid
Stability:	The test substance was stable under the conditions of the study based on analytical results.
Study Initiated/Completed:	October 14, 2005 / (see report cover page)
Experimental Start/Termination:	October 19, 2006 / February 1, 2007

SUMMARY

The purpose of this study was to evaluate the potential of ammonium perfluorooctanoate (APFO (linear)) to suppress the primary humoral immune response following exposure via oral gavage for up to 28 consecutive days. Groups of 20 male mice each were administered the test substance at daily levels of 0, 0.3, 1, 10, 30, and 30/0 mg/kg. The group designated 30/0 mg/kg day was included to assess potential reversibility/recovery and was therefore administered the test substance for 23 consecutive days followed by 6 consecutive days of vehicle (water) administration. Body weights, food consumption measurements, and clinical observations were recorded during the in-life period. Prior to sacrifice, the immune system was stimulated by injecting sheep red blood cells (SRBC) on test day 24 and blood samples were collected from each mouse on test day 29. The serum samples were assayed for their concentration of SRBC-specific IgM antibody to provide a quantitative assessment of humoral immune response. Serum from animals similarly challenged with cyclophosphamide, a positive control immunosuppressive agent, was analyzed concurrently to provide confirmation that the assay performance was acceptable for detection of immunosuppression. Clinical pathology data were collected at test day 29 and assessed effects on hematology and clinical chemistry. At sacrifice, each animal was examined grossly and selected organs were weighed (brain, spleen, and thymus); selected tissues (as outlined in the methods section) were retained and examined histologically. Thymus and spleen cells were manually counted from single-cell suspensions prepared from the collected tissue.

Samples of the dosing formulations were chemically analyzed and the results indicated that the test substance was at the targeted concentrations, homogeneously mixed, and stable under the conditions of the study.

Test substance-related toxicity was observed during the in-life portion of the study at 1 mg/kg and higher. Adverse reductions in body weights, weight changes, food consumption, and food efficiency occurred at 10 mg/kg and higher; at 30 and 30/0 mg/kg, these reductions were accompanied by low incidences of clinical observations indicative of toxicity. Effects on body weight and food consumption parameters were detected at 1 mg/kg, but these reductions were not considered adverse. There were no test substance-related effects observed at 0.3 mg/kg during the in-life portion of the study.

Mice dosed with ≥1 mg/kg had decreased serum HDL cholesterol, increased serum albumin, and variable changes in serum globulin. Mice dosed with ≥10 mg/kg had increased neutrophils and monocytes, decreased eosinophils, icteric serum, decreased serum total cholesterol, non-HDL cholesterol, and triglycerides, and increased serum corticosterone. Mice dosed with 30 mg/kg also had decreased red cell mass parameters (red blood cell count, hemoglobin, and hematocrit), increased reticulocytes, and decreased lymphocytes. The only parameter with complete recovery in the 30/0 mg/kg group was non-HDL cholesterol. Partial recovery was observed for icteric serum, total and HDL cholesterol, triglycerides, and serum corticosterone.

Test substance-related organ weight effects were observed in the liver, spleen, and thymus. Mean liver weight parameters were increased at ≥0.3 mg/kg, mean spleen weight parameters were decreased at ≥1 mg/kg, and mean thymus weight parameters were decreased at ≥10 mg/kg.

Test substance-related gross observations were observed at doses ≥10 mg/kg and included large and discolored livers, small spleens, and small thymuses.

Microscopic examination of the liver demonstrated mild hepatocellular hypertrophy at 0.3 mg/kg; moderate to severe hepatocellular hypertrophy with secondary individual cell necrosis and focal necrosis at doses ≥1 mg/kg; and increased hepatocellular mitotic figures, hepatocellular fatty change, and bile duct hyperplasia at doses ≥10 mg/kg.

Microscopic examination of lymphohematopoietic organs (spleen, thymus, bone marrow, lymph nodes) revealed increased granulocytic hematopoiesis in the bone marrow (≥10 mg/kg) and increased erythrocytic hematopoiesis in the bone marrow and spleen (30/0 mg/kg). Test substance-related lymphoid depletion/atrophy was present in the thymus (≥10 mg/kg) and spleen (30 mg/kg) of less than half of the mice at the respective dose levels. Mesenteric and popliteal lymph nodes had no test substance-related effects.

There was test substance-related evidence of immunosuppression in mice at 10, 30 and 30/0 mg/kg. The anti-SRBC titers for these groups were reduced 20, 28 and 30% when compared to the control group mean. There was no difference in mean primary humoral immune response between the 30 and 30/0 mg/kg, indicating that the shortened dosing period did not have an impact on this endpoint.

No significant changes in total thymus or spleen cell number were noted in animals dosed with 0.3 or 1 mg/kg. Significant decreases were noted in animals dosed with ≥10 mg/kg.

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for APFO for systemic toxicity in male mice was 0.3 mg/kg and for immunosuppression was 1 mg/kg.

INTRODUCTION

The primary objective of this study was to evaluate the potential of ammonium perfluorooctanoate (APFO (linear)) to suppress the primary humoral immune response to sheep red blood cells (SRBC) when administered by oral gavage to male mice for up to 28 consecutive days. Additional endpoints of toxicity were also evaluated. The oral route of administration was selected because it is a potential route of human exposure.

Ammonium perfluorooctanoate (APFO; FC-143, C_8; $C_7F_{15}COO^-NH_4^+$; CAS Registry number 3825-26-1) is a surfactant used as a processing aid in the production of fluoropolymers. Perfluorooctanoate (PFOA; $C_7F_{15}COO^-$), the dissociation product of APFO, is not metabolized[1] and has been identified in blood samples from exposed workers and the general population.[2,3,4]

PFOA has been reported to inhibit the ability of mice to make antibodies to a T-cell dependent antigen.[5] The reported study employed a single 0.02% APFO in chow (approximately 30 mg/kg) for 16 days. In order to better characterize the immune response following exposure to this material, APFO was administered by oral gavage using a broad range of doses.

Dosages for this study were selected based on the results of a 14-day oral gavage study in male rats and mice.[6]

STUDY DESIGN

A. Design Concentrations

Group	Number/ Group[a]	Daily Dosage (mg/kg)[b]	Dose Solution Concentration (mg/mL)[c]
I	20	0 (Control)	0
III	20	0.3	0.03
V	20	1	0.1
VII	20	10	1
IX	20	30	3
XI	20	30/0[d]	3

a Mice were divided into sub groups A and B (10/sub group) because of limited sample volume.
b Weight of test substance/kg or animal body weight.
c Solutions were adjusted for purity (19.5%).
d This group (XI) was dosed with 30 mg/kg of test substance through test day 23. Following injection of SRBC on test day 24, group XI was dosed with NANOpure® water, at a volume of 10 mL/kg of body weight, until sacrifice.

B. Study Overview

Study Parameters	Frequency
Body Weight	Day 0, 3 (2 for subgroup B), and daily thereafter
Food Consumption	Weekly
Daily Animal Health Observation	Twice daily
General Clinical Observation[a]	Day 0 and weekly thereafter
Detailed Clinical Observation	At each weighing
SRBC Injection	Prior to dosing (test day 24)
Clinical Pathology Evaluation	Test day 29
Serum Collection for Antibody Determination	At sacrifice (test day 29)
Anatomic Pathology Evaluation	Test day 29

a A check for acute signs of toxicity was conducted approximately 2 hours post-dosing.

MATERIALS AND METHODS

A. Test Guidelines

The study design complied with the following test guidelines:

- U.S. EPA, OPPTS 870.7800: Immunotoxicity, *Health Effects Test Guidelines* (1998)

B. Test Substance

(Appendix A)

APFO (linear), was supplied by the sponsor as a white to slightly opaque liquid in a 19.5% aqueous solution. The bulk test substance was used within the period of approved use as defined by the expiration date listed on the Certificate of Analysis (COA) that is provided in Appendix A. In addition, no evidence of instability, such as a change in color or physical state, was observed.

C. Test System

On October 6, 2005, 132 male Crl:CD(ICR) mice, with an assigned birth date of August 22, 2005, were received from Charles River Laboratories, Raleigh, North Carolina.

The Crl:CD(ICR) mouse was selected based on consistently acceptable health status and on extensive experience with this strain at Haskell Laboratory. By utilizing the Crl:CD(ICR) mouse, immunotoxicity studies can be conducted in the same strain that is used for other toxicology studies.

D. Animal Husbandry

1. Housing

All animals were housed singly in stainless steel, wire-mesh cages suspended above cage boards.

2. Environmental Conditions

Animal rooms were maintained at a temperature of 18-26°C and a relative humidity of 30-70%. Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle. Excursions outside of these ranges were of insufficient magnitude and/or duration to have adversely affected the validity of the study.

3. Feed and Water

All mice were provided tap water *ad libitum*. All mice were fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 *ad libitum*.

4. Animal Health and Environmental Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

E. Pretest Period

Upon arrival at Haskell Laboratory, all mice were housed in quarantine. The mice were:

- quarantined for 6 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.

- observed with respect to weight gain and any gross signs of disease or injury.

The mice were released from quarantine by the laboratory animal veterinarian or designee on the bases of acceptable body weights and clinical signs of all mice.

F. Assignment to Groups

Mice, selected on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury, were distributed by computerized, stratified randomization into study groups as designated in the Study Design, so that there were no statistically significant differences among group body weight means. The weight variation of selected mice did not exceed ± 20% of the mean weight.

At grouping, each mouse was assigned an animal number/cage identification number. Dose groups were subdivided into groups A and B, with 10 animals per group. The animal number/cage identification number were tattooed on the tail of each mouse and included on the cage label.

At study start (test day 0) the mice were approximately 8 weeks of age.

G. Dose Formulation Preparation and Administration

The dosing solutions were prepared in NANOpure® water. The formulations were adjusted based on the percentage of APFO in the bulk test substance to achieve the desired concentrations. Dosing formulations were prepared on a daily basis.

To accommodate the schedule of the laboratory, the initiation of dosing for group A mice was started one day prior to group B mice.

Animals were dosed daily at approximately the same time (± 2 hours) by intragastric intubation at a dose volume of 10 mL/kg body weight for at least 28 consecutive days; individual dose volumes were calculated based on the most recently collected body weight data. Control mice were dosed with NANOpure® water at a volume of 10 mL/kg of body weight. The 30/0 mg/kg group (XI) was dosed with 30 mL/kg of test substance through test day 23. Following injection of SRBC on test day 24, group XI was dosed with NANOpure® water at a volume of 10 mL/kg of body weight until sacrifice.

In light of marked body weight losses in some of the mice, a decision was made to suspend dosing for a few days with the intention of resuming dosing if the animals were sufficiently recovered. The table below lists the specific mice for which dosing was suspended as well as the test days on which the animals were not dosed. This protocol deviation did not adversely impact the study for several reasons: first, the suspension of dosing was transient and affected some but not all of the animals dosed at 30 mg/kg/day. Second, the data collected from animals dosed on a daily basis combined with the data from the animals listed below are considered to provide sufficient data to meet the objectives of the current study. Third, if suspension of dosing had not been implemented, unscheduled mortalities may have precluded the collection of immune system data in these animals and, thus, reduced the amount of data available to assess potential immunotoxicity.

Group	Animal Number	Test Days Not Dosed
IX (30 mg/kg)	901	9 - 11
XI (30/0 mg/kg)	1108	9 - 11
XI (30/0 mg/kg)	1109	9 - 11
XI (30/0 mg/kg)	1117	8 - 10
XI (30/0 mg/kg)	1120	8 - 10

H. Dose Formulation Sampling and Analysis

1. Recovery Sample Analysis

Concurrent with dosing formulation analyses, recovery of APFO from spiked NANOpure® water was tested at the low level (approximately 0.03 mg/mL), the middle levels (approximately 0.1 and 1 mg/mL), and the high level (approximately 3 mg/mL) to confirm the analytical method. A stock solution of APFO was prepared in NANOpure® water. For all concentration levels, an appropriate aliquot of the stock solution was used to make the spiked solution upon further dilution with NANOpure® water. These spiked recovery samples were then processed and analyzed in the same manner as the dosing samples at similar concentrations.

2. Dosing Solution Treatment

Each dosing sample (1 mL) was initially diluted with NANOpure® water to a nominal concentration of 0.3, 1, 10, and 30 ppm APFO for the 0.03, 0.1, 1, and 3 mg/mL dosing samples, respectively. The samples were further diluted to a final expected concentration of 0.03 ppm with NANOpure® water for analysis. The 0 mg/mL sample followed the 0.03 mg/mL sample dilutions. Before the final dilution, the internal standard (1, 2-di-13C PFOA) was added to each sample to give an equivalent final concentration of the internal standard in all dosing samples; the 0.1, 1, and 3 mg/mL samples were matrix corrected with the initial diluted solution of the control sample.

3. Chromatographic Conditions

LC Parameters

Instrument: Agilent (Hewlett-Packard) 1100 liquid chromatograph
Column: Zorbax® RX-C8, 2.1 x 150 mm, 5 µm
Flow Rate: 0.4 mL/min
Oven Temperature: 35°C
Injection Volume: 20 µL
Mobile Phase: A) 0.15% Acetic acid in NANOpure® water
B) Acetonitrile

Gradient:	Time (min)	% Acetonitrile
	0	5
	0.9	5
	1.0	80
	5.0	80
	5.1	5
	7.0	5

MS Parameters

Instrument: Waters (Micromass) Quattro Micro
Ionization Mode: Electrospray (ESI), negative ion
Capillary Voltage: 2.7 kV
Cone Voltage: 15 V
Source Temperature: 120°C
Desolvation Temperature: 350°C
Scan Function: PFOA: 413 m/z (parent) to 369 m/z (daughter)
1, 2-di-13C PFOA: 415 m/z (parent) to 370 m/z (daughter)

4. Calibration and Quantitation

The analytical reference of APFO (H-22703-376, 100%) was used for quantitation of this study. A stock solution was prepared in NANOpure® water. This stock solution was mixed to ensure that all material was dissolved in solution. Before analysis, appropriate aliquots of the stock solution were diluted with NANOpure® water to make calibration standards that bracketed the target concentration of the diluted dosing samples after matrix correction with the initial diluted solution of the control sample. Before these aliquots were brought to the final volume, an appropriate amount of 1, 2-di-13C PFOA internal standard was added to give an equivalent final concentration of the internal standard in all standard solutions.

The 369 m/z daughter ion of PFOA dissociated from APFO measured by LC/MS/MS was used against the 370 m/z daughter ion of 1, 2-di-13C PFOA internal standard to determine the concentrations of the dosing samples. Peak area ratios (369 m/z peak versus 370 m/z peak) of these standards were used to construct a calibration curve by least square regression (see Figure 1 for a representative calibration curve). Measured concentrations for dosing solutions were determined by applying the peak area ratios from replicate injections of each sample to the calibration curve.

Concentration verification of APFO in dosing samples was evaluated by the mean result of the duplicate analyses for each respective dosing level.

Uniformity of mixing of APFO in dosing samples was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentration in the duplicate analyses of the concentration verification samples. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution.

Stability of APFO in dosing samples was evaluated by using the mean result of the duplicate concentration verification analyses as the baseline for comparing the corresponding stability results.

I. Body Weights

During the test period, all mice were weighed on test days 0, 3 (2 for subgroup B), and daily thereafter.

J. Food Consumption and Food Efficiency

During the test period, the amount of food consumed by each mouse over the weighing interval was determined by weighing each feeder at the beginning and end of the interval and subtracting the final weight and the amount of spillage from the feeder during the interval from the initial weight. From these measurements, mean daily food consumption over the interval was determined. From the food consumption and body weight data, the mean daily food efficiency of test substance was calculated for each animal.

K. Clinical Observations

1. Daily Animal Health Observations

Cage-site examinations to detect moribund or dead mice and abnormal behavior and/or appearance among mice were conducted at least once daily throughout the study. Abnormal behavior/appearance was recorded by exception. Moribund mice were sacrificed, and a gross examination performed. Tissues and blood were not collected from moribund mice.

2. General Clinical Observations

An additional cage-site evaluation was conducted approximately 2 hours after dosing to detect acute clinical signs of systemic toxicity.

3. Detailed Clinical Observations

At every weighing, each mouse was individually handled and examined for abnormal behavior and appearance. Detailed clinical observations in a standardized arena were also evaluated on all mice. The detailed clinical observations included (but were not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior. Any abnormal clinical signs noted were recorded.

L. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all surviving animals 29 days after initiation of the study. Animals from each dose group were divided into 2 groups, Group A and Group B with 10 animals in each (e.g., IA, IB, IIIA, IIIB). All animals were fasted for approximately 3 hours prior to the scheduled sacrifice. The fasting schedule was staggered so that the last animal

was fasted for approximately the same amount of time as the first animal. While the animals were under carbon dioxide anesthesia, the maximum amount of whole blood was collected from the abdominal *vena cava*. Samples were allocated as indicated below:

Group A	Group B
Hematology: 250 µL whole blood – EDTA Clinical Chemistry: remaining blood in serum tube for: total protein, albumin, globulin (calculated)	Not done Clinical Chemistry: all blood in serum tube for: Cholesterol, triglycerides, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol (calculated)

In addition, for all animals, remaining sera were allocated for either humoral immune measurements or for serum corticosterone based on the optimal use of the serum volume remaining in the tube after the above tests were performed.

Bone marrow smears were prepared at sacrifice from all surviving animals. Bone marrow smears were stained with Wright-Giemsa stain, but analysis was not necessary to support experimental findings. All blood samples were evaluated for quality by visual examination. Results were maintained in the study records and reported only if the sample was analyzed. Unless otherwise indicated, any historical control clinical pathology data referenced in the text is maintained in Haskell Notebook Number E 98560-AN.

1. Hematology (Group A Only)

Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-Giemsa-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination.

The following parameters were determined:

red blood cell count
hemoglobin
hematocrit
mean corpuscular (cell) volume
mean corpuscular (cell) hemoglobin
mean corpuscular (cell) hemoglobin concentration
red cell distribution width
absolute reticulocyte count
platelet count
white blood cell count
differential white blood cell count
microscopic blood smear examination

2. Clinical Chemistry

Routine serum clinical chemistry parameters were determined on an Olympus® AU640 clinical chemistry analyzer. Serum corticosterone was measured using a commercial RIA assay (Diagnostic Products Corporation, Los Angeles, CA; Catalog #TKRC1). Corticosterone concentrations were determined according to the manufacturer's recommended procedure

(aspirating aqueous contents of the assay tube rather than decanting). If necessary, the standard curve was extended at the low end of the range by including standards of 5 and 10 ng/mL.

The following parameters were determined:

cholesterol (group B)	globulin (calculated, group A)
triglycerides (group B)	high-density lipoprotein cholesterol (group B)
total protein (group A)	non-high-density lipoprotein cholesterol (calculated, group B)
albumin (group A)	serum corticosterone (groups A and B)

M. Humoral Immune Function

On test day 24, animals were injected intravenously in the lateral tail vein with 0.2 mL of 1×10^9 SRBC/mL (Covance, Denver, Pennsylvania, U.S.A.). One mouse (716 in the 10 mg/kg test substance group) was inadvertently not injected with the appropriate amount of SRBC and the immune response for this mouse could not be evaluated. On test day 29, serum was collected from each mouse and frozen (see L.2.Clinical Chemistry). Serum was not collected from 6 mice (117 in the 0 mg/kg test substance group, 306 in the 0.3 mg/kg test substance group, 903, 904, and 906 in the 30 mg/kg test substance group, and 1112 in the 30 mg/kg (recovery) test substance group) due to sacrifice *in extremis* prior to test day 29 (117, 906 and 1112), insufficient serum sample volume (306 and 904), or no serum sample taken (903); therefore, the immune response for these mice could not be evaluated. Serum volume was insufficient for 3 mice (703 in the 10 mg/kg test substance group, 907 in the 30 mg/kg test substance group, and 1116 in the 30 mg/kg (recovery) test substance group) and the immune response for these mice could not be evaluated.

Humoral immune function was evaluated by examining sera from individual animals for SRBC-specific IgM levels with an enzyme-linked immunosorbent assay (ELISA).[7] The serum from each animal was assayed as 10 serial, 2-fold dilutions, with 1 replicate per dilution. The optical density (OD) of the contents of the reaction well was measured at the 405 nm wavelength with a MR 5000 Microplate Reader (Dynex Technologies). SRBC-specific serum IgM titer data were analyzed with Revelation Software Version 2.0 (Dynex Technologies). For each serum sample, a semi-log graph of the data was created and the linear portion of the curve was identified by using a log-log curve fit. A slope between -0.600 and -1.200 was obtained. The serum dilution expected to produce an OD of 0.5 was determined by regression analysis. The "titer" of each animal was defined as the reciprocal of the serum dilution that had an OD value of 0.5. If no points had an OD value of greater than or equal to 0.5, the reciprocal of the starting dilution closest to an OD value of 0.5 was used as the titer.

Sera previously collected from rats injected with SRBC and dosed for 5 days with 90 mg/kg of the known immunosuppressive agent cyclophosphamide monohydrate or vehicle were run concurrently with the study samples to demonstrate that the assay functioned properly. For any test samples that needed to be rerun due to a poor curve fit or slope, pooled male and/or female cyclophosphamide monohydrate or vehicle serum samples were concurrently run. The pooled samples consisted of equal aliquots of serum taken from either the male or female rats dosed with cyclophosphamide monohydrate or vehicle.

N. Anatomic Pathology Evaluation

After 29 days on study, the surviving mice from each dose group (0, 0.3, 1, 10, 30, and 30/0 mg/kg body weight) were sacrificed and necropsied for evaluation of subchronic toxicity. The order of sacrifice for scheduled deaths was stratified across groups. Mice were fasted for 3 hours before euthanasia.

All mice, including 3 mice (mice 117, 906, and 1112) that were sacrificed *in extremis* during the study (test days 5, 9, and 5, respectively), were euthanized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed for all mice. Final body weights and organ weights were recorded for all mice sacrificed by design on test day 29.

The following tissues were collected from 120 mice (20/sex/group) on study.

Digestive System	Nervous System
liver[a]	brain[a,c] (3 sections)
Hematopoietic System	**Musculoskeletal System**
spleen[a]	femur/knee joint
thymus[a]	sternum
popliteal lymph node	
mesenteric lymph node	**Other**
bone marrow[b]	gross observations

a Organs were weighed at necropsy.
b Bone marrow was collected with the femur and sternum.
c Including cerebrum, cerebellum, medulla/pons.

Organ weight ratios (% final body weight, % brain weight) and group mean values from weighed organs were calculated.

All tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin (H&E), and examined microscopically by a veterinary pathologist. Microscopic findings were graded on a 4-point scale based on the severity or extent of the change (grade 1 = minimal; grade 2 = mild; grade 3 = moderate; grade 4 = severe).

For mice sacrificed by design (SD) on test day 29, all tissues collected from control (0 mg/kg) and high-dose (30 and 30/0 mg/kg) mice were processed to slides and examined microscopically. In addition, the following organs were examined from all SD mice in order to determine a no-observed-effect level for test substance-related microscopic findings: liver, thymus, spleen, and bone marrow.

For the 3 mice sacrificed *in-extremis* (SE) before the scheduled sacrifice, all tissues were processed to slides and examined microscopically.

Gross observations (recorded at necropsy) were examined microscopically for all animals.

O. Total Cell Counts

The following procedures were used for preparation of spleen and thymus single-cell suspensions for enumeration of total cell counts from each spleen or thymus:

- The weight of the halved spleen or thymus (tissue) was documented, the half was placed in a labeled 15 mL centrifuge tube containing 3 mL Hank's Balanced Salt Solution (HBSS/H) and put on ice.
- The halved tissue/HBSS/H was poured into a small petri dish and cut into small pieces.
- The centrifuge tube was inverted 2 or 3 times and left on ice for approximately 10 minutes to allow debris to settle to the bottom of the tube.
- The supernatant was transferred to a new centrifuge tube and the volume of the supernatant was documented.
- Total cell counts were determined from each tissue by hemacytometer.

P. Electron Microscopy Evaluation

A section of liver from 2 control mice (103 and 104) and 2 mice in the 1 mg/kg group (503 and 504) mice was placed in cassettes in a container of formalin, and shipped to Experimental Pathology Laboratories, Inc (EPL®) for evaluation by transmission electron microscopy. As a subcontractor to EPL®, the Laboratory for Advanced Electron and Light Optical Methods, College of Veterinary Medicine, North Carolina State University processed the tissues for electron microscopy and prepared electron photomicrographic images under the direction of Dr. Michael Dykstra. The printed electron photomicrographic images were provided to EPL® for evaluation by an ACVP-certified veterinary pathologist who interpreted the images and prepared a final report of the electron microscopic evaluation. More details are provided in Appendix M.

Q. Statistical Analyses

For all statistical analyses, significance was judged at $p < 0.05$. Comparisons were made of the dosed groups to the control group (Group I). Comparisons were also made between Group IX and Group XI.

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Humoral Immune Function Data[a] Clinical Pathology Organ Weights Total Cell Counts	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] followed by Dunnett's test[11,12,13]	Kruskal-Wallis test[14] followed by Dunn's test[15]

a SRBC-specific serum IgM antibody titer data were transformed to Log_2 to obtain normality or homogenous variances.

b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed by Dunn's test.

RESULTS AND DISCUSSION

Analytical Evaluation

A. Chromatography

(Figures 1-2)

PFOA dissociated from APFO and 1, 2-di-^{13}C PFOA eluted together from the HPLC column with a retention time of approximately 4.5 minutes. The mixture was separated into 2 resolved peaks at 369 m/z and 370 m/z, respectively, by MS/MS detection. Representative LC/MS/MS chromatograms are shown in Figures 2(a - e). Test substance was not detected in the 0 mg/mL samples.

B. Recovery Samples

(Table 1)

Detailed analytical results of recovery samples are summarized in Table 1. The variability of the analytical method was demonstrated by the coefficients of variation of the recovery results at each targeted dosing concentration (approximately 0.03, 0.1, 1, and 3 mg/mL) over the course of the study. The range of the measured concentrations of APFO for the 0.03 mg/mL level was 101.7% to 108.3% of nominal (mean percent recovery = 105.0% ± 5%, C.V. = 5%). The range of the measured concentrations of APFO for the 0.1 mg/mL level was 104.0% to 109.6% of nominal (mean percent recovery = 106.8% ± 4%, C.V. = 4%). The range of the measured concentrations of APFO for the 1 mg/mL level was 102.0% to 105.0% of nominal (mean percent recovery = 103.5 ± 2%, C.V. = 2%). The range of the measured concentrations of APFO for the 3 mg/mL level was 101.7% to 107.0% of nominal (mean percent recovery = 104.4 ± 4%, C.V. = 4%). Based on these data, the analytical method performed satisfactorily for the concentration range of the dosing samples in the study.

C. Concentration Verification, Uniformity of Mixing, and 5-Hour Room Temperature Stability Samples

(Table 2)

Dosing solutions prepared on October 17, 2005 were analyzed for concentration verification, uniformity of mixing, and 5-hour room temperature stability, and results are shown in Table 2.

The following table summarizes the results for concentration verification, uniformity of mixing, and 5-hour room temperature stability analyses.

Preparation Date	Nominal mg/mL	Measured[a] mg/mL	Average % Nominal	C.V. (%)	Stability[b] % Nominal
17-October-05	0	ND[c]	---	---	---
	0.03	0.0278, 0.0277	92.7	0.3	96.3
	0.1	0.0966, 0.0979	97.3	0.9	99.0
	1	0.979, 1.04, 1.03[d]	102.0	3	96.9
	3	3.16, 3.06	103.7	2	102.0

a Duplicate samples analyzed.
b Stability samples held for 5 hours at room temperature.
c Denotes not detected.
d Data obtained from one of the duplicate initial analyses and 2 repeats from the re-diluted sample.

The data for samples submitted on October 17, 2005 show that the test substance was at the targeted levels (± 7.3% of nominal), uniformly mixed (CV's = 0.3%, 0.9%, 3%, and 2%, respectively), and stable when held for 5 hours at room temperature in the vehicle. Test substance was not detected in the 0 mg/mL sample.

D. Concentration Verification and Uniformity of Mixing Samples

(Table 3)

Dosing solutions prepared on November 15, 2005 were analyzed for concentration verification and uniformity of mixing, and results are shown in Table 3.

The following table summarizes the results for concentration verification and uniformity of mixing analyses.

Preparation Date	Nominal mg/mL	Measured[a] mg/mL	Average % Nominal	C.V. (%)
15-November-05	0	ND[b]	---	---
	0.03	0.0276, 0.0272	91.3	1
	0.1	0.0954, 0.0986	97.0	2
	1	1.02, 1.01	102.0	0.7
	3	3.21, 3.23	107.3	0.4

a Duplicate samples analyzed.
b Denotes not detected.

The data for samples submitted on November 15, 2005 show that the test substance was at the targeted levels (± 8.7% of nominal) and uniformly mixed (CV's = 1%, 2%, 0.7%, and 0.4%, respectively). Test substance was not detected in the 0 mg/mL sample.

E. Analytical Conclusions

Data from the analyses of the samples collected during the study indicate that the dosing formulations were at the targeted concentrations, mixed uniformly, and stable under the conditions of the study. Test substance was not found in the 0 mg/mL samples

In-Life Measurements

A. Mean Body Weights and Body Weight Gains

(Tables 4-5, Figure 3, Appendices B-C)

Test substance-related and adverse reductions in mean body weights and body weight gains were observed at 10, 30 and 30/0 mg/kg.

Mean final body weights were 14, 22, and 12% lower than the control group at 10, 30, and 30/0 mg/kg, respectively. Test substance-related increases in liver weights occurred and minimized the magnitude of the effects on body weight. In an attempt to quantitatively separate the increased liver weights (see Appendix C) from the decreased body weights, an adjusted body weight (see Appendix C) was calculated for each animal by subtracting the weight of the liver from the final body weight. The means for the adjusted body weights were 28, 35, and 23% lower than controls at 10, 30, and 30/0 mg/kg, respectively.

The reductions in mean body weight at 10 mg/kg and above resulted from overall body weight losses during the study; mice lost an average of 3.8, 6.6, and 3.3 g during days 0 to 28 at 10, 30, and 30/0 mg/kg, respectively, whereas control group mice gained an average of 0.9 g.

In general, the test substance-related effects on body weight parameters were dose-related relative to the magnitude of the change and the onset of the reductions; effects on mice dosed at 30 mg/kg were more pronounced and evident sooner than effects at 10 mg/kg.

The effects of cessation of dosing were evident in that the mean final body weights of mice at 30/0 mg/kg were 12% higher than those from the mice dosed at 30 mg/kg.

Body weight and weight gain data for animals dosed at 0.3 and 1 mg/kg were generally comparable to controls.

B. Food Consumption and Food Efficiency

(Tables 6-7, Appendix D)

Test substance-related effects on food consumption were evident at 10, 30, and 30/0 mg/kg. The food consumption data did not adhere to the hypothesis of a monotonic dose response. At 10 mg/kg, the mean food consumption was increased or significantly increased starting at the end of the first week and persisting until the end of the study. At 30 and 30/0 mg/kg, mean food consumed was usually lower or significantly lower than controls but for each group there was one interval with significantly increased food consumption. As a result of these somewhat erratic patterns of food consumption, overall food consumption during days 0 to 28 was generally comparable across the groups with the exception of the 10 mg/kg group for which mean food consumption was significantly increased.

C. Clinical Observations and Mortality

(Tables 8-9, Appendices E-F)

Test substance-related clinical signs observed at 1, 10, 30 and 30/0 mg/kg included: pallor, wet and stained fur, swollen penis, eye observations, prostrate, or yellow extremities.

Swollen left shoulder observed in one mouse dosed at 10 mg/kg was possibly due to a dosing incident.

Abnormal gait was observed in single animals dosed at 1 or 10 mg/kg. This observation was not considered test substance related because it was only observed in single animals and short in duration.

Three mice were sacrificed *in extremis* prior to test day 29. Two mice were sacrificed on test day 5 due to dosing incidents from the control and 30/0 mg/kg groups. One mouse dosed at 30 mg/kg was sacrificed on test day 9 possibly due to a dosing incident, however, gross and microscopic pathology were unable to determine the exact cause of death

Clinical Pathology Evaluation

A. Hematology

(Table 10, Appendix G)

1. Red Blood Cells

Red cell mass parameters (red blood cell count, hemoglobin, and hematocrit) were minimally decreased in mice dosed with 30 mg/kg for 29 days. Mean values were 88-94% of the control group means (not statistically significant). In addition, mean cell hemoglobin and mean cell hemoglobin concentration were decreased in mice dosed with 10 or 30 mg/kg for 29 days. Means at 10 and 30 mg/kg were 94-96% and 95-97% of the respective control group means for these 2 parameters (variable statistical significance).

Some mice dosed with 1 or 10 mg/kg for 29 days had minimally lower reticulocyte counts compared to those dosed with 0 or 0.3 mg/kg. Mice dosed with 30 mg/kg either had higher (3/7) or lower (4/7) reticulocyte counts compared to control mice. Two of the 3 mice at 30 mg/kg with higher reticulocyte counts also had increased splenic extramedullary hematopoiesis. On an individual animal basis, there was no correlation between red cell mass and reticulocyte counts in this group.

Effects on red cell mass were more pronounced (mildly decreased) in mice dosed with 30/0 mg/kg compared to those dosed with 30 mg/kg for the entire 29 days. At recovery, mean red blood cell count, hemoglobin, and hematocrit ranged from 82-86% of the respective control group means for these 3 parameters (all statistically significant). Decreased red cell mass parameters following recovery could be due to one or more of the following processes: increased red cell destruction, red cell loss, or increased plasma volume. The mechanism for

decreased red cell mass parameters was not evident from in-life, clinical pathology, or anatomic pathology data. Therefore, the cause of the decreased red cell mass was not determined.

Reticulocytes were mildly increased in mice dosed with 30/0 mg/kg. Mean reticulocyte count was 148% of the control group mean (not statistically significant). Consistent with the increase in reticulocyte counts, red cell distribution width was increased (mean was 109% of the control group mean; not statistically significant), and mean cell hemoglobin concentration was decreased (97% of control group mean; statistically significant). Microscopically, this group had increased polychromasia (increased bluish staining of red blood cells), a characteristic finding in blood with increased reticulocyte counts. The increases in reticulocytes and related parameters were considered to be in response to the decreased red cell mass described above. These changes also correlated with histologic evidence of increased splenic extramedullary hematopoiesis, which was observed in 15 of 19 mice in the 30/0 mg/kg group.

2. White Blood Cells

Neutrophils were increased in mice dosed with 10 or 30 mg/kg. Means were 236 and 296% of the control group mean, respectively (statistically significant). While all neutrophil counts for mice dosed with ≤1 mg/kg were between 0.00 and $2.00x10^3/\mu L$, mice dosed with 10 mg/kg had neutrophil counts between 1.00 and $3.00x10^3/\mu L$, while 2 of 7 mice dosed with 30 mg/kg had neutrophil counts of greater than $3.50x10^3/\mu L$ (animal 901 and 904). Histologically, 2 of 3 mice (mice 902 and 904) dosed with 30 mg/kg had minimal granulocytic hyperplasia of the bone marrow, corresponding to the observation of increased neutrophils in the peripheral blood of this group. The two 30 mg/kg mice with the highest neutrophil counts (901 and 904) also had higher lymphocyte and monocyte counts than other mice in this group, although the lymphocyte counts were similar to or lower than control values. Increased neutrophils may be due to stress (glucocorticoid-related; see corticosterone discussion below and anatomic pathology) or inflammation. The changes in neutrophils, in light of changes in other leukocyte types, are likely related to both of these processes.

Lymphocytes were generally decreased in mice dosed with 30 mg/kg (mean was 59% of the control group mean; not statistically significant). One mouse (animal 901) had increased neutrophil and unchanged lymphocyte counts compared to control mice. The decreases in lymphocyte counts in most mice dosed with 30 mg/kg were consistent with stress (see corticosterone discussion below and histology), and corresponded to increased serum corticosterone and lymphoid depletion/atrophy in the spleen, thymus, and lymph nodes in 30 mg/kg mice. The unchanged lymphocyte count in 1 mouse dosed with 30 mg/kg may have been due to a combination of stress and inflammation.

Monocytes were increased in mice dosed with 10 or 30 mg/kg. Means were 285 and 254% of the control group mean, respectively (variable statistical significance). In these 2 groups of mice, individual mice with increased monocytes tended to have increased neutrophil counts. Increased monocytes are observed with inflammation or stress. As discussed above, the combination of changes likely reflect both stress and inflammation.

Eosinophils were decreased in mice dosed with 10 or 30 mg/kg. Means were 57 and 64% of the control group mean, respectively (not statistically significant). A decrease in peripheral blood

eosinophils is consistently observed in response to stress. Therefore, this change was considered to be due to stress.

Large unstained cells (LUC) were increased in mice dosed with 10 or 30 mg/kg. LUCs are cells that cannot be identified as one of the 5 major leukocyte types by the Advia 120 automated hematology analyzer, and normally comprise a small percentage of the total leukocyte population. The LUC count normally includes mostly lymphocytes and monocytes. In this study, the mice with the highest LUC counts usually had the highest lymphocyte and/or monocyte counts. Therefore, in this study, changes in LUC counts paralleled changes in lymphocytes and/or monocytes.

In the 30/0 mg/kg group, neutrophil, lymphocyte, eosinophil, monocyte, and LUC counts were generally similar to those of mice dosed at 30 mg/kg for the full 29 days (variable statistical significance compared to controls; lymphocyte counts statistically different from that of mice dosed with 30 mg/kg for 29 days). Therefore, there was little or no recovery for changes in differential white blood cell counts.

The following statistically significant changes in mean hematology parameters were considered to be unrelated to treatment and non-adverse because they did not occur in a dose-related pattern:

- Decreased mean cell hemoglobin concentration in mice dosed with 10 mg/kg for 29 days
- Decreased red cell distribution width in mice dosed with 0.3 or 10 mg/kg for 29 days
- Increased total white blood cell count in mice dosed with 10 mg/kg for 29 days

B. Clinical Chemistry

(Table 11, Appendix G)

Icterus was evident in serum of mice dosed with 10 or 30 mg/kg for 29 days. The incidences of icteric serum were 0/19, 0/19, 0/20, 16/20, and 17/17 in mice dosed with 0, 0.3, 1, 10, or 30 mg/kg for 29 days. Icterus is graded as none, trace, small, moderate, or large and in this study, grades of trace, small and moderate were observed. The icterus grades were generally higher at 30 than at 10 mg/kg. Icterus is an indication of increased serum bilirubin and may result from either increased production of bilirubin from hemoglobin as a result of increased red blood cell destruction or decreased processing and excretion of bilirubin. There was no clinical or anatomic pathology evidence of increased red cell destruction in mice dosed for 29 days. Histologically, minimal to mild hyperplasia of the bile ducts were observed in mice dosed with 10 or 30 mg/kg, which, along with other hepatic changes, may have contributed to the presence of icterus. In mice dosed in the 30/0 mg/kg group, the incidence and grades of icterus were lower than after 29 days of treatment (trace to small icterus observed in 16/19 mice). Therefore, there was partial recovery from the finding of icteric serum.

Total cholesterol was moderately decreased in mice dosed with 10 or 30 mg/kg for 29 days. Means were 69 and 51% of the control group means (statistically significant). The decrease in cholesterol was due to decreases in HDL cholesterol at doses of 1, 10 and 30 mg/kg (means were 71, 61, and 44% of the control group mean, respectively, and were statistically significant), and

in non-HDL cholesterol at doses of 10 and 30 mg/kg (means were 85 and 65% of the control group mean, respectively; not statistically significant). Mean total and HDL cholesterol in the 30/0 mg/kg group were 80% and 69% of the control group mean (variable statistical significance compared to control but statistically different from mice dosed with 30 mg/kg for 29 days). Therefore, there was partial recovery of total and HDL cholesterol, and complete recovery for non-HDL cholesterol in mice dosed with 30/0 mg/kg.

Triglycerides were moderately decreased in mice dosed with 10 or 30 mg/kg for 29 days. Means were 47 and 32% of the control group mean, respectively (statistically significant). There was partial recovery of triglycerides, as the mean value in mice in the 30/0 mg/kg group was 57% of the control group mean (statistically different from control mice and mice dosed with 30 mg/kg for 29 days).

Albumin was moderately increased in mice dosed with 1, 10, or 30 mg/kg for 29 days (means were 110, 145, and 131% of the control group mean, respectively; variable statistical significance). Although albumin data were limited to 3 values at 30 mg/kg for 29 days, albumin concentrations for these 3 mice were greater than those of mice dosed with 0.3 or 1 mg/kg, suggesting a treatment-related increase. Increased albumin may result from dehydration (relative increase) or increased synthesis or decreased catabolism (absolute increase). There were no in-life or clinical pathology data to support dehydration; however, urine concentration, an important sign of dehydration, was not evaluated in this study. Some peroxisome proliferator-activated receptor (PPAR) agonists have been reported to cause increases in serum albumin concentration due to increased synthesis of albumin. Due to the lack of corroborative data, the cause of increased albumin in this study cannot be determined. In the 30/0 mg/kg group, albumin concentrations were similar to those of mice dosed for 10 or 30 mg/kg for 29 days and were increased compared to those of control mice. Therefore, there was no recovery in albumin concentrations.

Globulin concentrations were increased in the 30/0 mg/kg group compared to those of control mice and mice dosed with 30 mg/kg for 29 days (both statistically significant; mean was 119% of the control mean), suggesting a test substance-related effect.

Total protein measurements include albumin and globulin, so changes in total protein are a function of changes in these 2 components. Total protein concentration was increased at 10 mg/kg (due to increases in albumin) and similar to control values at 30 mg/kg (due to increases in albumin and decreases in globulin). Means for these 2 groups were 125 and 109% of the control group mean, respectively (variable statistical significance). In the 30/0 mg/kg group, total protein was 134% of the control group mean (due to increases in both albumin and globulin).

Serum corticosterone was moderately increased in several mice dosed with 10 or 30 mg/kg for 29 days (variable statistical significance). While serum corticosterone concentrations were between 0 and 400 ng/mL in all mice dosed with ≤1 mg/kg, concentrations greater than 400 ng/mL were observed in 7/10 and 6/10 mice dosed with 10 or 30 mg/kg, respectively, resulting in mean concentrations that were 229 and 231% of the control group mean for mice for these 2 groups. In the 30/0 mg/kg group, mouse serum corticosterone concentrations were still mildly increased (6/10 were greater than 400 ng/mL, and the mean was 137% of the control

group mean; not statistically significant). These changes are consistent with partial recovery from stress.

C. Clinical Pathology Conclusions

Mice dosed with ≥1 mg/kg had decreased serum HDL cholesterol, increased serum albumin, and variable changes in serum globulin. Mice dosed with ≥10 mg/kg had increased neutrophils and monocytes, decreased eosinophils, icteric serum, decreased serum total cholesterol, non-HDL cholesterol, and triglycerides, and increased serum corticosterone. Mice dosed with 30 mg/kg also had decreased red cell mass parameters (red blood cell count, hemoglobin, and hematocrit), increased reticulocytes, and decreased lymphocytes. The only parameter with complete recovery in the 30/0 mg/kg group was non-HDL cholesterol. Partial recovery was observed for icteric serum, total and HDL cholesterol, triglycerides, and serum corticosterone.

Immunotoxicity

A. Humoral Immune Function

(Tables 12-13, Appendices H-I)

There was test substance-related evidence of immunosuppression in mice at 10, 30 and 30/0 mg/kg. The anti-SRBC titers for these groups were reduced 20, 28 and 30% when compared to the control group mean.

There was no difference in mean primary humoral immune response between the 30 and 30/0 mg/kg, indicating that the shortened dosing period did not have an impact on this endpoint.

In contrast, mice injected for 5 days with 90 mg/kg of the immunosuppressive material, cyclophosphamide, demonstrated a 52% inhibition of the IgM antibody response to SRBC.

Anatomic Pathology Evaluation

A. Cause of Death

There were no test substance-related deaths. Only 3 of the 120 mice on study did not survive until the scheduled sacrifice on day 29. The 3 mice were sacrificed *in extremis* on test days 5 and 9.

Mouse 117 (control) and mouse 1112 (30/0 mg/kg) were sacrificed on test day 5 due to dosing incidents. Both mice had ruptured esophagi identified on gross examination. Mouse 906 (30 mg/kg) was sacrificed on test day 9 because the mouse was clinically lethargic and pale. Gross and microscopic pathology did not reveal a cause of death. It is likely that this death was also due to a dosing incident. However, since the esophagus, lungs, and mediastinal tissue were not saved for microscopic examination, the cause of death was undetermined.

B. Final Body and Organ Weight Data

(Table 14, Appendix J)

Following 28 days of daily gavage administration of the test substance, test substance-related organ weight effects were observed in the liver, spleen, and thymus. Relative to controls, mean liver weight parameters were increased at ≥0.3 mg/kg, mean spleen weight parameters were decreased ≥1 mg/kg, and mean thymus weight parameters were decreased at ≥10 mg/kg.

Text Table 1: Mean Absolute and Relative (% body weight) Organ Weights in Male Mice

Group:	I	III	V	VII	IX	XI
Dose (mg/kg):	0	0.3	1	10	30	30/0
Number of Mice/Sex:	19	20	20	20	19	19
Final Body Wt. (g)	33.0	33.4	33.8	28.4*	26.0*	30.5*^
Liver	(17)	(20)	(20)	(20)	(18)	(18)
absolute wt. (g)	1.782	2.407	3.272**	6.061**	5.899**	6.391**
% body wt.	5.421	7.196	9.704**	21.232**	22.618**	21.209**
Spleen	(19)	(20)	(20)	(20)	(19)	(19)
absolute wt. (g)	0.117	0.116	0.104	0.066**	0.052**	0.076**
% body wt.	0.355	0.346	0.307*	0.232*	0.195*	0.249*
Thymus	(19)	(20)	(20)	(20)	(19)	(19)
absolute wt. (g)	0.050	0.045	0.049	0.025**	0.025**	0.027**
% body wt.	0.153	0.137	0.144	0.087**	0.094**	0.088**

wt. = weight; ( ) number in parenthesis is the number of organs weighed.
Underlined values were interpreted to be test-substance related effects, as compared to control values.
* = statistically significant (Dunnett/Tamhane-Dunnett parametric pairwise test), compared to control value.
** = statistically significant (Dunn's non-parametric pairwise test), compared to control value.
^ = statistically significant (Dunn's non-parametric pairwise test) change in Group XI value compared to Group IX value.

1. Final Body Weight

Mean final body weights were decreased 14%, 21%, and 8% in the 10, 30, and 30/0 mg/kg dose groups, respectively, as compared to the control value. All decreases were statistically significant. Mean final body weights in the 0.3 and 1 mg/kg dose groups were similar to the control values.

There was also a statistically significant increase in the mean final body weight of the 30/0 mg/kg dose group, as compared to the 30 mg/kg dose group. This increase demonstrates partial recovery from the test substance-related final body weight decrease in the 6 recovery days following the injection of sheep red blood cells.

2. Liver

Mean absolute liver weights were increased 35%, 84%, 240%, 231%, and 259% in the 0.3, 1, 10, 30, and 30/0 mg/kg dose groups, respectively, as compared to the control value. Mean relative (% body weight) liver weights were similarly increased (33%, 79%, 292%, 317%, and 291%, respectively). All increases were statistically significant, except for those in the 0.3 mg/kg dose group.

The increased liver weights, at all dose levels, correlated with the microscopic finding of mild to severe hepatocellular hypertrophy. It also correlated with the gross observation of large livers at doses ≥10 mg/kg.

3. Spleen

Mean absolute spleen weights were decreased 11%, 44%, 56%, and 35% in the 1, 10, 30, and 30/0 mg/kg dose groups, respectively, as compared to the control value. Mean relative (% body weight) spleen weights were similarly decreased (14%, 35%, 45%, and 30%, respectively). All decreases were statistically significant, except for the increase in the mean absolute spleen weight in the 1 mg/kg dose group. Mean spleen weight parameters in the 0.3 mg/kg dose group were similar to the control values.

The decreased spleen weights, at ≥1 mg/kg, correlated with the microscopic finding of minimal to mild lymphoid depletion/atrophy in this organ. It also correlated with the gross observation of small spleens at doses ≥10 mg/kg.

4. Thymus

Mean absolute thymus weights were decreased 50%, 50%, and 46% in the 10, 30, and 30/0 mg/kg dose groups, respectively, as compared to the control value. Mean relative (% body weight) thymus weights were similarly decreased (43%, 39%, and 42%, respectively). All decreases were statistically significant. Mean thymus weight parameters in the 0.3 and 1 mg/kg dose groups were similar to the control values.

The decreased thymus weights, at ≥10 mg/kg, correlated with the microscopic finding of minimal to severe lymphoid depletion/atrophy in this organ. It also correlated with the gross observation of small thymuses at doses ≥10 mg/kg.

5. Other

All other individual and mean organ weight differences were considered to be spurious or secondary to the decrease in final body weights. Mean absolute brain weights were decreased, while mean relative brain weights (% body weight) were increased only at doses (≥10 mg/kg) that produced significantly decreased body weights. The lack of any gross or microscopic effects on the brain also suggests that the brain weight differences were a function of body weight and not indicative of a test substance-relate brain weight effect.

C. Gross Observations

(Table 15 Appendix K)

At the terminal sacrifice, test substance-relate gross observations were observed at doses ≥10 mg/kg and included large and discolored livers, small spleens, and small thymuses.

Text Table 2: Incidences of Test Substance-Related Gross Observations in Male Mice

Group:	I	III	V	VII	IX	XI
Dose (mg/kg):	0	0.3	1	10	30	30/0*
Number of Mice/Group:	19**	20	20	20	19**	19**
Liver						
Large	1	0	0	17	16	17
Discoloration	0	0	0	1	5	1
Spleen						
Small	0	0	0	8	8	2
Thymus						
Small	0	0	0	3	2	2

Underlined values were interpreted to be test-substance related increases, as compared to control values.
* Not dosed with test substance following immunology challenge.
** Table excludes 3 mice that were euthanized on days 5 (mice #s 117 and 1112) and 9 (mouse #906).

The observation of large livers in mice given ≥10 mg/kg correlated with the microscopic finding of severe hepatocellular hypertrophy in all mice at these dosages and greater than 200% increases in mean absolute liver weights, as compared to controls. Gross liver discoloration is also consistent with microscopic hepatocellular hypertrophy.

Small spleens, which were observed in almost half of the spleens from mice given 10 (8/20) and 30 (8/19) mg/kg of the test substance, correlated with decreased mean spleen weights at these same dose levels. Fewer small spleens (2/19) were observed in the recovery group (30/0 mg/kg), which was consistent with the partial recovery of spleen weights in this dose group. Test substance-related microscopic lymphoid depletion was observed only at 30 mg/kg.

Small thymuses were recorded in only a few thymuses at dose levels ≥10 mg/kg. These correlated with decreased mean thymus weights and microscopic lymphoid depletion at the same dose levels.

D. Microscopic Findings

(Table 16, Appendix K)

Microscopic examination of the liver demonstrated mild hepatocellular hypertrophy at 0.3 mg/kg; moderate to severe hepatocellular hypertrophy with secondary individual cell necrosis and focal necrosis at doses ≥1 mg/kg; and increased hepatocellular mitotic figures, hepatocellular fatty change, and bile duct hyperplasia at doses ≥10 mg/kg

Microscopic examination of lymphohematopoietic organs (spleen, thymus, bone marrow, lymph nodes) revealed increased granulocytic hematopoiesis in the bone marrow (≥10 mg/kg) and increased erythrocytic hematopoiesis in the bone marrow and spleen (30/0 mg/kg). Test substance-related lymphoid depletion/atrophy was present in the thymus (≥10 mg/kg) and spleen (30 mg/kg) of less than half of the mice at the respective dose levels. Mesenteric and popliteal lymph nodes had no test substance-related effects.

Text Table 3: Incidences of Test Substance-Related Microscopic Findings in Male Mice

Group:	I	III	V	VII	IX	XI
Dose (mg/kg):	0	0.3	1	10	30	30/0*
Number of Mice/Group:	19**	20	20	20	19**	19**
Liver	(19)	(20)	(20)	(20)	(19)	(19)
Hypertrophy, hepatocellular	0	20 [2.0]	20 [3.0]	20 [4.0]	19 [4.0]	19 [4.0]
Necrosis, individual cell	0	0	11 [1.1]	20 [1.9]	19 [2.0]	19 [1.7]
Necrosis, focal	0	1 [1.0]	3 [1.0]	4 [1.8]	7 [1.9]	3 [1.7]
Mitotic figures, increased	0	0	0	10 [1.0]	15 [1.0]	19 [1.4]
Hyperplasia, bile duct	0	0	0	6 [1.0]	17 [1.2]	12 [1.0]
Fatty change, nonzonal	0	0	0	9 [1.0]	14 [1.0]	4 [1.0]
Thymus	(19)	(20)	(19)	(19)	(17)	(19)
Depl./Atr. Lymph. or NP.	0	0	0	8 [1.6]	12 [2.9]	6 [2.8]
Spleen	(19)	(20)	(20)	(20)	(19)	(19)
Depletion/Atrophy, lymphoid	0	1 [1.0]	0	0	8 [1.1]	7 [1.1]
EMH, increased	6 (1.2)	4 [1.5]	1 [1.0]	3 [1.7]	5 [1.2]	15 [1.8]
Bone Marrow	(19)	(20)	(20)	(20)	(19)	(19)
Hyperplasia, granulocytic	0	0	0	3 [1.7]	4 [1.0]	3 [1.7]
Hyperplasia, erythrocytic	0	0	0	0	0	3 [2.0]

[ ] = Number in brackets is the average grade (grades 1 – 4) when lesion is present (i.e., sum of grades ÷ # animals with lesion). Grading scale: 1 = minimal; 2 = mild; 3 = moderate; 4 = severe.
( ) number in parenthesis is the number of organs weighed; EMH = Extramedullary hematopoiesis.
Underlined values were interpreted to be test-substance related increases, as compared to control values.
* Not dosed with test substance following immunology challenge.
** Table excludes 3 mice that were euthanized on days 5 (mice #s 117 and 1112) and 9 (mouse #906).
. Includes lymphoid depletion/atrophy and thymus not present in mediastinal tissue (assumed grade 3 atrophy).

1. Liver

a. Hepatocellular Hypertrophy

Panlobular hepatocellular hypertrophy was observed in all surviving mice given the test substance and the severity was dose related. Hypertrophy was present in 0/19, 20/20, 20/20, 20/20, 19/19, and 19/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. The hypertrophy was graded as mild in all mice given 0.3 mg/kg, moderate in all mice given 1 mg/kg; and severe in all mice given ≥10 mg/kg.

The hepatocellular hypertrophy was characterized by an increase in the size of all hepatocytes due to an increase in cytoplasmic volume. The cytoplasm had a uniformly eosinophilic granular appearance consistent with peroxisome proliferation. At doses ≥1 mg/kg, the severity (moderate to severe) of the hepatocellular hypertrophy appeared to be responsible for increased individual cell necrosis and focal necrosis. At doses ≥10 mg/kg, the severity (severe) of the hepatocellular hypertrophy was associated with nonzonal fatty change and hepatocellular regeneration (increased mitotic figures).

Hepatocellular hypertrophy correlated with increased mean liver weight parameters at all doses and grossly large livers at doses ≥10 mg/kg.

b. Individual Cell Necrosis

Individual cell necrosis was observed in mice given ≥1 mg/kg of the test substance; the incidence and severity were dose related. Individual cell necrosis was present in 0/19, 0/20, 11/20, 20/20, 19/19, and 19/19 in mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively, and was graded minimal to mild. A slight decrease in severity was apparent in the 30/0 mg/kg group as compared to the 30 mg/kg group.

The individual cell necrosis was primarily due to the degeneration, necrosis, and lysis of enlarged hepatocytes in an individualized, non-zonal pattern. Although apoptotic cells were observed in most sections, the increased individual cell necrosis was usually not due to apoptosis. A slight secondary focal inflammatory cell inflitrate was often observed in association with necrotic hepatocytes.

c. Focal Necrosis

Test substance-related focal necrosis was also observed in mice given ≥1 mg/kg of the test substance. The incidence and severity were both mildly dose related. Focal necrosis was present in 0/19, 1/20, 3/20, 4/20, 7/19, and 3/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively, and was graded minimal to moderate. The single incidence of minimal focal necrosis in a 0.3 mg/kg mouse was considered incidental since this is sometimes a naturally occurring background lesion. A slight decrease in the incidence of focal necrosis was apparent in the 30/0 mg/kg group, as compared to the 30 mg/kg group.

Focal necrosis was characterized by the focal or multifocal coagulative necrosis of a cluster of hepatocytes. The distribution was usually subcapsular and the pattern was non-zonal. Focal coagulative necrosis of hepatocyte clusters is a common secondary effect of hepatocellular hypertrophy and is most likely the result of secondary focal ischemia.[16]

d. Increased Mitotic Figures

Increased mitotic figures were observed in mice given ≥10 mg/kg of the test substance; the incidence was dose related. Increased mitotic figures were present in 0/19, 0/20, 0/20, 10/20, 15/19, and 19/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively, and was graded minimal to mild. A slight increase in the incidence and severity was apparent in the 30/0 mg/kg group, as compared to the 30 mg/kg group.

Increased mitotic figures were an apparent indication of increased cell turnover in those mice with severe hepatocellular hypertrophy and subsequent individual cell necrosis.

e. Bile Duct Hyperplasia

Bile duct hyperplasia was observed in mice given ≥10 mg/kg and the incidence and severity were both dose related. Bile duct hyperplasia was observed in 0/19, 0/20, 0/20, 6/20, 17/19, and 12/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. The hyperplasia was graded as minimal in all mice except for three 30 mg/kg mice which were graded as mild. A slight decrease in the incidence of bile duct hyperplasia was apparent in the 30/0 mg/kg group, as compared to the 30 mg/kg group.

The bile duct hyperplasia was characterized by a minimal to mild increase in the number of profiles of normal bile ducts.

f. Fatty Change, Nonzonal

Nonzonal fatty change was also present in mice given ≥10 mg/kg. The incidence was dose related but all lesions were graded as minimal. Fatty change was observed in 0/19, 0/20, 0/20, 9/20, 14/19, and 4/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. A decrease in the incidence of fatty change was apparent in the 30/0 mg/kg group, as compared to the 30 mg/kg group.

The fatty change was characterized by a minimal increase in the number of hepatocytes with small to medium size cytoplasmic fatty globules. The distribution of the affected hepatocytes was nonzonal as the fatty change was scattered throughout the liver. The fatty change was only observed in livers with severe diffuse hepatocellular hypertrophy and was considered to be a degenerative change secondary to the hypertrophy.

2. Thymus

a. Lymphoid Depletion/Atrophy

Minimal to severe thymic lymphoid depletion/atrophy was only observed in mice given ≥10 mg/kg. The lesion was present in 0/19, 0/20, 0/19, 6/19, 7/17, and 4/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. In addition, thymic tissue was not present in the mediastinal tissue section of 9 other mice (given ≥10 mg/kg), suggesting that these animals also had moderate to severe thymic lymphoid depletion. Therefore, the combined incidence of lymphoid depletion and absent thymic tissue was 0/19, 0/20, 0/19, 8/19, 12/17, and 6/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. Both the incidence and severity were dose related. A slight decrease in the incidence and severity of thymic lymphoid depletion/atrophy was apparent in the 30/0 mg/kg group, as compared to the 30 mg/kg group.

Thymic lymphoid depletion/atrophy was characterized by decrease in the number of lymphocytes in the thymus in the absence of necrotic cells. As stated earlier, the absence of thymic tissue in the mediastinal tissue section was also interpreted to be indicative of thymic depletion/atrophy.

3. Spleen

a. Lymphoid Depletion/Atrophy

Minimal to mild splenic lymphoid depletion/atrophy was test substance related only at 30 mg/kg. The lesion was present in 0/19, 1/20, 0/20, 0/20, 8/19, and 7/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. The incidence and severity of this effect was similar in the 30 and 30/0 mg/kg groups.

As with the thymic lesion, splenic lymphoid depletion/atrophy was characterized by a decrease in the number of lymphocytes in the thymus in the absence of necrotic cells.

b. Increased Extramedullary Hematopoiesis

An increase in the incidence of splenic extramedullary hematopoiesis (EMH) was considered test substance related only in high-dose mice allowed a recovery period (30/0 mg/kg dose group). Minimal to moderate increased EMH was observed in 6/19, 4/20, 1/20, 3/20, 5/19, and 15/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively.

The increased splenic EMH was erythrocytic and correlated with both the bone marrow erythrocytic hyperplasia and the hematological finding of decreased red cell mass parameters and increased circulating reticulocytes (see Clinical Pathology) that were also observed only in the 30/0 mg/kg recovery mice.

4. Bone Marrow

a. Granulocytic Hyperplasia

A minimal to moderate increase in bone marrow granulocytic hyperplasia was observed in 0/19, 0/20, 0/20, 3/20, 4/19, and 3/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively. The incidence and severity were not dose related in groups given ≥10 mg/kg of the test substance.

The increase in bone marrow granulocytic hyperplasia (≥10 mg/kg) correlated with increases in the peripheral white blood cell and neutrophil counts (see Clinical Pathology). The granulocytic response was most likely secondary to the hepatocellular individual cell necrosis and focal necrosis observed in mice given ≥1 mg/kg of the test substance.

b. Erythrocytic Hyperplasia

A mild increase in bone marrow erythrocytic hyperplasia was observed only in high-dose mice allowed a recovery period (30/0 mg/kg dose group). Erythrocytic hyperplasia was observed in 0/19, 0/20, 0/20, 0/20, 0/19, and 3/19 mice given 0, 0.3, 1, 10, 30, and 30/0 mg/kg, respectively.

As discussed for the spleen, the increase in bone marrow erythrocytic hyperplasia in recovery mice correlated with both microscopic splenic EMH and hematology findings (decreased red cell mass parameters and increased circulating reticulocytes (see Clinical Pathology)).

5. Other

All other microscopic observations in this study were consistent with normal background lesions in mice of this age and strain.

E. Ultrastructural Findings

1. Electron Microscopy Evaluation

(Appendix M)

At the 1 mg/kg dose of APFO (linear), an increase in peroxisomes was not observed. However, many organelles could not be clearly identified due to poor ultrastructural detail, which was likely the result of formalin fixation. Therefore, definitive conclusions on perosimal numbers in treated groups relative to controls could not be drawn. More details are provided in Appendix M.

F. Anatomic Pathology Conclusions

There were no test substance-related deaths. Only 3 of the 120 mice on study did not survive until the scheduled sacrifice on day 29. The 3 mice were sacrificed *in extremis* on test days 5 and 9.

Following 28-days of daily gavage administration of the test substance, test substance-related organ weight effects were observed in the liver, spleen, and thymus. Mean liver weight parameters were increased, mean spleen weight parameters were decreased, and mean thymus weight parameters were decreased.

At the terminal sacrifice, test substance-relate gross observations were observed at doses ≥10 mg/kg and included large and discolored livers, small spleens, and small thymuses.

Microscopic examination of the liver demonstrated mild hepatocellular hypertrophy at 0.3 mg/kg; moderate to severe hepatocellular hypertrophy with secondary individual cell necrosis and focal necrosis at doses ≥1 mg/kg; and increased hepatocellular mitotic figures, hepatocellular fatty change, and bile duct hyperplasia at doses ≥10 mg/kg

Microscopic examination of lymphohematopoietic organs (spleen, thymus, bone marrow, lymph nodes) revealed increased granulocytic hematopoiesis in the bone marrow (≥10 mg/kg) and increased erythrocytic hematopoiesis in the bone marrow and spleen (30/0 mg/kg). Test substance-related lymphoid depletion/atrophy was present in the thymus (≥10 mg/kg) and spleen (30 mg/kg) of less than half of the mice at the respective dose levels. Mesenteric and popliteal lymph nodes had no test substance-related effects.

Total Cell Counts

A. Spleen Cell Number

(Table 17, Appendix L)

No significant changes in total spleen cell number were noted in animals dosed with 0.3 or 1 mg/kg. Significant decreases were noted in animals dosed with 10 mg/kg or greater, with the greatest suppression compared to vehicle-treated controls observed at 30 mg/kg (63% suppression). In the 30/0 mg/kg group, a rebound was seen (44% suppression), but this increase in cells compared to the 30 mg/kg was most likely due to the extramedullary hematopoiesis observed in 15 of 19 mice in this treatment group.

B. Thymus Cell Number

(Table 17, Appendix L)

No significant changes in total thymus cell number were noted in animals dosed with 0.3 or 1 mg/kg. Significant decreases were noted in animals dosed with 10 mg/kg or greater, with the greatest suppression observed at 30 mg/kg (82% suppression). In the 30/0 mg/kg group, a rebound was seen (51% suppression).

CONCLUSIONS

Under the conditions of this study, the no-observed-adverse-effect level (NOAEL) for APFO for systemic toxicity in male mice was 0.3 mg/kg and for immunosuppression was 1 mg/kg.

RECORDS AND SAMPLE STORAGE

Specimens (if applicable), raw data, the protocol, amendments (if any), and the final report will be retained at Haskell Laboratory, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware.

Laboratory-specific raw data such as personnel files, instrument, equipment, refrigerator and/or freezer raw data will be retained at the facility where the work was done.

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TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular (cell) volume
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell
-	-	no data
NC	-	not calculated or not calculable

Summary of Clinical Chemistry Values

CHOL	-	cholesterol
TRIG	-	triglycerides
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
HDL	-	high-density lipoprotein cholesterol
NHDL	-	non-high-density lipoprotein cholesterol
SCORT	-	serum corticosterone

NOTES:

Summary of Hematology Values
Summary of Clinical Chemistry Values
Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

TABLES

EXPLANATORY NOTES (Continued)

NOTES: (Continued)

Summary of Total Cell Counts

$$\text{Organ Weight as Percent of Body Weight} = \frac{\text{Organ Weight (g)}}{\text{Final Body Weight (g)}} \times 100$$

$$\text{Total Number of of Organ Cells } (\times 10^8) = \frac{\text{Organ Weight (g)}}{\text{Half Organ Weight (g)}} \times \text{Organ Cell Suspension Volume (mL)} \times \text{Number of Cells in Half Organ } (\times 10^6 \text{ cells/mL}) \div 100$$

Table 1
Recovery of APFO Added to Dosing Vehicle

Sample Type	APFO (mg/mL)		Percent
	Nominal	Measured	Nominal
RECOVERY[A]	0.0302	0.0327	108.3
RECOVERY[B]	0.0300	0.0305	101.7
		Mean	***105.0 ± 5, C.V. 5%***
RECOVERY[A]	0.104	0.114	109.6
RECOVERY[B]	0.100	0.104	104.0
		Mean	***106.8 ± 4, C.V. 4%***
RECOVERY[A]	1.00	1.02	102.0
RECOVERY[B]	1.00	1.05	105.0
		Mean	***103.5 ± 2, C.V. 2%***
RECOVERY[A]	3.00	3.05	101.7
RECOVERY[B]	3.00	3.21	107.0
		Mean	***104.4 ± 4, C.V. 4%***

(A) Processed with dosing samples submitted October 17, 2005 for concentration verification, uniformity of mixing, and 5-hour room temperature stability analyses.
(B) Processed with dosing samples submitted November 15, 2005 for concentration verification and uniformity of mixing analyses.

Table 2
Concentration Verification, Uniformity of Mixing, and 5-Hour Room Temperature Stability of APFO in Dosing Solutions

Sample Date / Sample Type[A]	APFO (mg/mL) Nominal		Measured	Percent Nominal
15-November-2005				
Concentration Verification				
Control	0		ND[B]	----
#1	0.03		0.0278	92.7
#2	0.03		0.0277	92.3
		Mean:	***0.0278 ± 0.0001***	***(92.7)***
			C.V. 0.3%	
#1	0.1		0.0966	96.6
#2	0.1		0.0979	97.9
		Mean:	***0.0973 ± 0.0009***	***(97.3)***
			C.V. 0.9%	
#1	1		0.979	97.9
#1[C]	1		1.04	104.0
#2[C]	1		1.03	103.0
		Mean:	***1.02 ± 0.03***	***(102.0)***
			C.V. 3%	
#1	3		3.16	105.3
#2	3		3.06	102.0
		Mean:	***3.11 ± 0.07***	***(103.7)***
			C.V. 2%	
Stability[D]				
	0.03		0.0289	96.3
	0.1		0.0990	99.0
	1		0.969	96.9
	3		3.06	102.0

(A) Duplicate analyses per level performed for concentration verification. Mean, S.D. and C.V. calculated to verify uniformity of mixing.
(B) Denotes not detected.
(C) Duplicate analyses from the re-diluted sample.
(D) Samples held at room temperature for 5 hours.

Table 3
Concentration Verification and Uniformity of Mixing of APFO in Dosing Solutions

Sample Type[A] / Sample Date	APFO (mg/mL) Nominal		Measured	Percent Nominal
Concentration Verification				
11-October-2005				
Control	0		ND[B]	----
#1	0.03		0.0276	92.0
#2	0.03		0.0272	90.7
		Mean:	***0.0274 ± 0.0003***	***(91.3)***
			C.V. 1%	
#1	0.1		0.0954	95.4
#2	0.1		0.0986	98.6
		Mean:	***0.0970 ± 0.002***	***(97.0)***
			C.V. 2%	
#1	1		1.02	102.0
#2	1		1.01	101.0
		Mean:	***1.02 ± 0.008***	***(102.0)***
			C.V. 0.7%	
#1	3		3.21	107.0
#2	3		3.23	107.7
		Mean:	***3.22 ± 0.01***	***(107.3)***
			C.V. 0.4%	

(A) Duplicate analyses per level performed for concentration verification. Mean, S.D. and C.V. calculated to verify uniformity of mixing.
(B) Denotes not detected.

Table 4
Mean Body Weights of Male Mice

DAYS ON TEST	MEAN BODY WEIGHTS (g) Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
0	32.4 1.7(20)	32.4 1.8(20)	32.6 1.8(20)	32.3 1.7(20)	32.7 2.2(20)	32.7 1.6(20)
7	32.8 1.6(19)	32.6 1.8(20)	32.7 1.7(20)	31.8 2.3(20)	28.1* 3.1(20)	28.1* 3.1(19)
14	33.0 1.8(19)	33.0 1.9(20)	33.1 2.0(20)	29.7* 2.3(20)	28.6* 2.9(19)	28.0* 2.7(19)
21	33.7 1.5(19)	33.8 2.0(20)	34.2 1.8(20)	29.2* 2.0(20)	26.0* 3.1(19)	26.0* 2.8(19)
28	33.4 1.5(19)	33.9 2.5(20)	34.2 1.8(20)	28.6* 2.1(20)	26.2* 3.0(19)	29.5*† 3.4(19)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 5
Mean Body Weight Gains of Male Mice

	MEAN BODY WEIGHT GAINS (g)					
DAYS ON TEST	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
0-7	0.2 0.7(19)	0.3 0.9(20)	0.0 1.0(20)	-0.5 1.6(20)	-4.6@ 3.0(20)	-4.7@ 2.7(19)
7-14	0.3 0.8(19)	0.3 0.5(20)	0.4 0.8(20)	-2.1@ 1.6(20)	0.2 3.0(19)	-0.0 2.9(19)
14-21	0.7 0.7(19)	0.8 0.4(20)	1.1 0.9(20)	-0.5@ 1.4(20)	-2.6@ 3.5(19)	-2.0@ 3.0(19)
21-28	-0.3 0.7(19)	0.1 0.8(20)	0.0 0.8(20)	-0.6 0.9(20)	0.3 1.7(19)	3.4@† 2.5(19)
OVERALL 0-28	0.9 1.4(19)	1.5 1.8(20)	1.5 1.9(20)	-3.8* 1.9(20)	-6.6* 3.5(19)	-3.3* 2.6(19)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 6
Mean Daily Food Consumption by Male Mice

	MEAN DAILY FOOD CONSUMED PER ANIMAL (g)					
DAYS ON TEST	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
7	5.1 0.4(19)	5.1 0.4(20)	5.2 0.4(20)	5.0 0.6(20)	4.5 0.8(20)	4.5* 0.7(19)
14	5.1 0.4(19)	5.2 0.4(20)	5.3 0.5(20)	5.8* 0.8(20)	5.6* 0.8(19)	5.5 1.0(19)
21	5.1 0.4(19)	5.1 0.4(20)	5.1 0.5(20)	5.3 0.9(20)	4.4@ 1.2(18)	4.6† 0.9(19)
28	4.7 0.5(19)	4.9 0.4(20)	5.2 0.4(20)	5.5@ 0.8(20)	4.8 1.1(19)	5.5@† 1.3(19)
OVERALL 0-28	5.0 0.3(19)	5.1 0.3(20)	5.2 0.3(20)	5.4@ 0.5(20)	4.9 0.9(18)	5.0 0.7(19)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 7
Mean Daily Food Efficiency of Male Mice

	MEAN DAILY FOOD EFFICIENCY (g weight gain/g food consumed)					
DAYS ON TEST	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
0-7	0.005 0.020(19)	0.008 0.026(20)	0.001 0.028(20)	-0.020 0.053(20)	-0.161@ 0.122(20)	-0.165@ 0.116(19)
14	0.006 0.023(19)	0.009 0.015(20)	0.010 0.020(20)	-0.057@ 0.050(20)	0.004 0.082(19)	-0.003 0.071(19)
21	0.019 0.019(19)	0.023 0.011(20)	0.031 0.026(20)	-0.014@ 0.040(20)	-0.103@ 0.148(18)	-0.065@† 0.091(19)
28	-0.010 0.021(19)	0.001 0.023(20)	-0.000 0.022(20)	-0.017 0.023(20)	0.008 0.056(19)	0.087@ 0.056(19)
OVERALL 0-28	0.006 0.010(19)	0.010 0.012(20)	0.011 0.013(20)	-0.026* 0.015(20)	-0.053* 0.032(18)	-0.025* 0.021(19)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 8
Summary of Daily Animal Health Observations in Male Mice

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group IX 30/0 mg/kg (Recovery)
ANIMAL COUNT:	20	20	20	20	20	20
Enophthalmus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Abnormal Gait	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Feces Absent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Lethargic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Not Eating	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Stained Cageboard	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Swollen Shoulder	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (5%)	0 (0%)
Swollen Penis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)

Data arranged as: number of animals (percent of group) for which an observation was recorded

Table 9
Summary of Detailed Clinical Observations in Male Mice

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group IX 30/0 mg/kg (Recovery)
ANIMAL COUNT:	20	20	20	20	20	20
Absent End of tail	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Eye Dark	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Enophthalmus	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Eye Partially Closed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Wet Fur	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
Prostrate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Abnormal Gait	1 (5%)	0 (0%)	1 (5%)	1 (5%)	0 (0%)	0 (0%)
Pale	0 (0%)	0 (0%)	0 (0%)	1 (5%)	4 (20%)	0 (0%)
Feces Absent	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Labored Breathing	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lethargic	1 (5%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (5%)
Not Eating	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)

Table 9
Summary of Detailed Clinical Observations in Male Mice (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group IX 30/0 mg/kg (Recovery)
ANIMAL COUNT:	20	20	20	20	20	20
Misshapen Tail	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
Stain Fur/Skin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (5%)
Stained Cageboard	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Swollen Neck	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Swollen Face	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Swollen Shoulder	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)
Swollen Penis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)

Data arranged as: number of animals (percent of group) for which an observation was recorded

Table 10
Summary of Hematology Values for Male Mice

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
RBC ($x10^6/\mu L$)						
DAY 29	10.23	10.15	9.30	10.04	9.64	8.82@
	0.72(10)	0.38(10)	1.43(10)	0.97(8)	0.89(7)	0.77(9)
HGB (g/dL)						
DAY 29	16.0	15.8	14.3	14.9	14.1	13.1@
	1.1(10)	0.5(10)	2.2(10)	1.7(8)	1.9(7)	1.2(9)
HCT (%)						
DAY 29	53.0	52.7	48.0	51.9	48.3	45.0@
	3.3(10)	1.9(10)	7.4(10)	5.0(8)	6.1(7)	3.5(9)
MCV (fL)						
DAY 29	51.8	51.9	51.7	51.7	49.9	51.1
	2.1(10)	1.4(10)	1.9(10)	2.6(8)	2.0(7)	2.2(9)
MCH (pg)						
DAY 29	15.6	15.6	15.4	14.9	14.6*	14.8
	0.5(10)	0.6(10)	0.7(10)	1.0(8)	0.7(7)	0.6(9)
MCHC (g/dL)						
DAY 29	30.1	30.1	29.8	28.7*	29.1	29.1*
	0.7(10)	1.1(10)	0.8(10)	1.0(8)	0.7(7)	1.0(9)

Table 10
Summary of Hematology Values for Male Mice (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
RDW (%)						
DAY 29	12.9	12.3@	12.2	12.1@	13.1	14.0
	0.3(10)	0.3(10)	0.7(10)	0.5(8)	0.8(7)	2.2(9)
ARET (x10³/μL)						
DAY 29	326.5	342.3	274.8	248.2	350.4	481.9
	27.9(10)	53.4(10)	65.3(10)	62.1(8)	160.1(7)	207.6(9)
PLT (x10³/μL)						
DAY 29	1177	1402	1176	-	-	1501
	NC(1)	202(2)	315(5)			723(4)
WBC (x10³/μL)						
DAY 29	7.55	9.57	8.90	11.14*	6.75	7.29
	2.39(10)	2.84(10)	2.62(10)	2.24(8)	2.61(7)	1.06(9)
ANEU (x10³/μL)						
DAY 29	0.80	1.29	0.96	1.89*	2.37*	2.05*
	0.42(10)	0.46(10)	0.49(10)	0.60(8)	1.14(7)	0.57(9)
ALYM (x10³/μL)						
DAY 29	6.43	7.82	7.60	8.67	3.81	4.78†
	1.92(10)	2.66(10)	2.57(10)	2.08(8)	1.39(7)	0.77(9)

Table 10
Summary of Hematology Values for Male Mice (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
AMON ($x10^3/\mu L$)						
DAY 29	0.13	0.16	0.11	0.37@	0.33	0.23
	0.09(10)	0.11(10)	0.07(10)	0.18(8)	0.23(7)	0.14(9)
AEOS ($x10^3/\mu L$)						
DAY 29	0.14	0.18	0.14	0.08	0.09	0.09
	0.10(10)	0.07(10)	0.08(10)	0.04(8)	0.07(7)	0.08(9)
ABAS ($x10^3/\mu L$)						
DAY 29	0.01	0.02	0.02	0.02	0.02	0.02
	0.02(10)	0.01(10)	0.01(10)	0.02(8)	0.02(7)	0.04(9)
ALUC ($x10^3/\mu L$)						
DAY 29	0.04	0.09	0.06	0.10	0.14	0.11
	0.05(10)	0.05(10)	0.04(10)	0.11(8)	0.11(7)	0.12(9)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 11
Summary of Clinical Chemistry Values for Male Mice

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
CHOL (mg/dL)						
DAY 29	117	128	101	81*	60*	94#
	29(9)	38(10)	30(10)	23(10)	22(10)	22(9)
TRIG (mg/dL)						
DAY 29	167	148	157	78*	53*	96*#
	37(9)	41(10)	41(10)	31(10)	27(10)	23(9)
TP (g/dL)						
DAY 29	5.6	5.2	5.6	7.0*	6.1	7.5*#
	0.3(6)	0.5(7)	0.4(8)	0.3(7)	0.8(3)	0.7(9)
ALB (g/dL)						
DAY 29	2.9	2.8	3.2	4.2*	3.8*	4.3*#
	0.2(6)	0.3(7)	0.1(8)	0.3(7)	0.3(3)	0.4(9)
GLOB (g/dL)						
DAY 29	2.7	2.4	2.5	2.8	2.3	3.2*#
	0.2(6)	0.3(7)	0.4(8)	0.1(7)	0.5(3)	0.4(9)
HDL (mg/dL)						
DAY 29	77	77	55*	47*	34*	53*#
	19(9)	13(10)	15(10)	11(10)	11(10)	11(9)

Table 11
Summary of Clinical Chemistry Values for Male Mice (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
NHDL (mg/dL)						
DAY 29	40	51	46	34	26	41#
	10(9)	27(10)	18(10)	14(10)	13(10)	13(9)
SCORT (ng/mL)						
DAY 28-29	189	198	108	433*	437	259
	112(10)	86(10)	76(10)	156(10)	278(10)	168(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
\# Statistically significant difference from Group IX at $p < 0.05$ by t-test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 12
Summary of Primary Humoral Immune Response to SRBC for Male Mice Dosed with APFO

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
LOG_2[a]	9.027 0.587(19)[b]	8.819 0.787(19)[b]	8.310 0.619(20)	7.185@ 1.351(18)[c,d]	6.513@ 1.037(16)[b,c]	6.277@ 0.680(18)[b,c]

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Mean log2 of the serum IgM titer data.
b Serum was not collected from one or more animals, therefore, immune response could not be evaluated for these animals.
c Serum volume was insufficient for one or more animals, therefore, immune response could not be evaluated for these animals.
d One or more animal was not injected with the appropriate amount of SRBC, therefore, immune response could not be evaluated for these animals.

@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

Table 13
Summary of Primary Humoral Immune Response to SRBC for Male Mice Dosed With Positive Control

	Saline[a]	Cyclophosphamide 90 mg/kg[a]	Saline[b]	Cyclophosphamide 90 mg/kg[b]
LOG_2	8.603 0.685(10)	4.515 0.843(10)	8.662	5.129

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Mean log_2 of the SRBC-specific serum IgM titer data for individual samples.
b Log_2 of the SRBC-specific serum IgM titer data for pooled samples.

Table 14
Mean Final Body and Organ Weights from Male Mice

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)						
LIVER	1.782 0.175(17)[a]	2.407 0.255(20)	3.272@ 0.231(20)	6.061@ 1.320(20)	5.899@ 0.850(18)[b]	6.391@ 1.505(18)[b]
SPLEEN	0.117 0.015(19)	0.116 0.032(20)	0.104 0.016(20)	0.066@ 0.019(20)	0.052@ 0.023(19)	0.076@ 0.022(19)
THYMUS	0.050 0.010(19)	0.045 0.010(20)	0.049 0.012(20)	0.025@ 0.009(20)	0.025@ 0.013(19)	0.027@ 0.010(19)
BRAIN	0.471 0.027(19)	0.478 0.029(20)	0.474 0.029(20)	0.446* 0.028(20)	0.440* 0.026(19)	0.442* 0.029(19)
FINAL BODY WEIGHT (grams)						
	33.0 1.3(19)	33.4 2.5(20)	33.8 1.8(20)	28.4* 2.0(20)	26.0* 2.8(19)	30.5*† 3.7(19)

Table 14
Mean Final Body and Organ Weights from Male Mice (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)						
LIVER/ FINAL BODY * 100	5.421 0.466(17)[a]	7.196 0.418(20)	9.704@ 0.736(20)	21.232@ 3.715(20)	22.618@ 2.614(18)[b]	21.209@ 4.835(18)[b]
SPLEEN/ FINAL BODY * 100	0.355 0.045(19)	0.346 0.082(20)	0.307* 0.043(20)	0.232* 0.062(20)	0.195* 0.067(19)	0.249* 0.058(19)
THYMUS/ FINAL BODY * 100	0.153 0.034(19)	0.137 0.034(20)	0.144 0.035(20)	0.087@ 0.031(20)	0.094@ 0.048(19)	0.088@ 0.027(19)
BRAIN/ FINAL BODY * 100	1.427 0.080(19)	1.436 0.091(20)	1.408 0.103(20)	1.576* 0.111(20)	1.703* 0.132(19)	1.467† 0.189(19)

Table 14
Mean Final Body and Organ Weights from Male Mice (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)						
LIVER/ BRAIN * 100	379.673 34.913(17)[a]	503.340 46.491(20)	691.370@ 55.479(20)	1357.057@ 275.001(20)	1336.969@ 167.426(18)[b]	1457.734@ 345.770(18)[b]
SPLEEN/ BRAIN * 100	24.915 2.950(19)	24.226 6.087(20)	21.872* 3.312(20)	14.822* 4.260(20)	11.756* 4.890(19)	17.267*† 4.669(19)
THYMUS/ BRAIN * 100	10.758 2.438(19)	9.533 2.207(20)	10.199 2.245(20)	5.592@ 2.072(20)	5.638@ 2.969(19)	6.164@ 2.278(19)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a An error occurred while weighing livers for 2 animals in this group, and the liver weights were excluded from calculations.
b Liver inadvertently not weighed from one animal in this group.

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
† Statistically significant difference from Group IX at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; significant differences between IX and XI were detected.

Table 15
Incidence of Gross Observations in Male Mice

LESIONS	TREATMENT per day	LESION INCIDENCE (Numeric) 0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
		I	III	V	VII	IX	XI
LIVER		(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED		19	20	20	3	3	3
LARGE.		1			17	16	17
DISCOLORATION					1	6	1
SPLEEN		(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED		20	20	20	12	12	18
SMALL.					8	8	2
THYMUS		(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED		20	20	20	17	18	18
SMALL.					3	2	2
POPLITEAL LYMPH NODE		(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED		20	20	20	20	20	20
MESENTERIC LYMPH NODE		(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED		20	20	20	20	19	20
SMALL.						1	
BRAIN		(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED		20	20	20	20	20	20

Figures in parentheses are the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

Table 15
Incidence of Gross Observations in Male Mice (Continued)

LESIONS	LESION INCIDENCE (Numeric)					
TREATMENT per day	0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
	I	III	V	VII	IX	XI
FEMUR/KNEE JOINT	(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED	20	20	20	20	20	20
STERNUM	(20)	(20)	(20)	(20)	(20)	(20)
NO ABNORMALITY DETECTED	20	20	20	20	20	20
PENIS					(1)	
PARAPHIMOSIS.					1	
SKIN	(1)			(1)		(1)
MASS, GREEN, AXILLA, LEFT.				1		
OTHER, ABSCESS AXILLA RIGHT.						1
OTHER, abscess subcutaneous axilla right, subcutaneous air pocket, dorsal neck, right axilla.	1					
ESOPHAGUS	(1)					(1)
RUPTURE.	1					1
TRACHEA	(1)					
RUPTURE.	1					

Figures in parentheses are the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

Table 16
Incidence and Lesion Grades of Microscopic Observations in Male Mice

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC) 0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
		I	III	V	VII	IX	XI
LIVER		(19)	(20)	(20)	(20)	(19)	(19)
NO ABNORMALITY DETECTED		17					
NECROSIS, INDIVIDUAL CELL, INCREASED.							
minimal				10	3		6
mild				1	17	19	13
Total observations per lesion				11	20	19	19
NECROSIS, FOCAL.							
minimal			1	3	2	4	2
mild					1		
moderate					1	3	1
Total observations per lesion			1	3	4	7	3
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR.							
minimal					10	15	12
mild							7
Total observations per lesion					10	15	19
INFLAMMATION, SUBACUTE/CHRONIC.							
minimal			1	1	4	1	5
Total observations per lesion			1	1	4	1	5

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
Table excludes 3 mice that were euthanized on test days 5 (mice 117 or 1112) and 9 (mouse 906).

Table 16
Incidence and Lesion Grades of Microscopic Observations in Male Mice (Continued)

LESIONS	LESION INCIDENCE (NUMERIC)					
TREATMENT per day	0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
	I	III	V	VII	IX	XI
LIVER	(19)	(20)	(20)	(20)	(19)	(19)
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR.						
mild		20				
moderate			20			
severe				20	19	19
Total observations per lesion		20	20	20	19	19
HYPERPLASIA, BILE DUCT.						
minimal				6	14	12
mild					3	
Total observations per lesion				6	17	12
HEMATOPOIESIS, EXTRAMEDULLARY.						
minimal						1
Total observations per lesion						1
FATTY CHANGE, DIFFUSE.						
minimal	1					
mild	1					
Total observations per lesion	2					
FATTY CHANGE, NONZONAL.						
minimal				9	14	4
Total observations per lesion				9	14	4

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
Table excludes 3 mice that were euthanized on test days 5 (mice 117 or 1112) and 9 (mouse 906).

Table 16
Incidence and Lesion Grades of Microscopic Observations in Male Mice (Continued)

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC) 0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
		I	III	V	VII	IX	XI
SPLEEN		(19)	(20)	(20)	(20)	(19)	(19)
NO ABNORMALITY DETECTED		13	15	19	17	9	4
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY.							
minimal		5	2	1	1	4	4
mild		1	2		2	1	10
moderate							1
Total observations per lesion		6	4	1	3	5	15
DEPLETION/ATROPHY, LYMPHOID.							
minimal			1			7	6
mild						1	1
Total observations per lesion			1			8	7
THYMUS		(19)	(20)	(19)	(19)	(17)	(19)
NO ABNORMALITY DETECTED		19	20	18	11	5	12
HYPERPLASIA, LYMPHOID, FOLLICULAR.							
mild				1			
Total observations per lesion				1			

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
Table excludes 3 mice that were euthanized on test days 5 (mice 117 or 1112) and 9 (mouse 906).

Table 16
Incidence and Lesion Grades of Microscopic Observations in Male Mice (Continued)

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC) 0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
		I	III	V	VII	IX	XI
THYMUS		(19)	(20)	(19)	(19)	(17)	(19)
DEPLETION/ATROPHY, LYMPHOID.							
minimal					5	1	1
mild					1	2	
moderate						1	2
severe						3	1
Total observations per lesion					6	7	4
CYST, EPITHELIAL.							
minimal							2
Total observations per lesion							2
NOT PRESENT IN MEDIASTINAL TISSUE.					2	5	2
ECTOPIC THYROID.		1			1		
LYMPH NODE - POPLITEAL		(10)				(18)	(19)
NO ABNORMALITY DETECTED		6				14	5
NOT PRESENT IN TISSUE SECTION.		4				4	14
MESENTERIC LYMPH NODE		(19)	(20)	(19)	(20)	(19)	(19)
NO ABNORMALITY DETECTED		19	20	19	19	16	18
DEPLETION/ATROPHY, LYMPHOID.							
mild						1	
Total observations per lesion						1	

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
Table excludes 3 mice that were euthanized on test days 5 (mice 117 or 1112) and 9 (mouse 906).

Table 16
Incidence and Lesion Grades of Microscopic Observations in Male Mice (Continued)

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC) 0 mg/kg	0.3 mg/kg	1 mg/kg	10 mg/kg	30 mg/kg	30/0 mg/kg Recovery
		I	III	V	VII	IX	XI
MESENTERIC LYMPH NODE		(19)	(20)	(19)	(20)	(19)	(19)
NOT PRESENT IN TISSUE SECTION.					1	2	1
BONE MARROW		(19)	(20)	(20)	(20)	(19)	(19)
NO ABNORMALITY DETECTED		19	20	20	17	15	13
HYPERPLASIA, GRANULOCYTIC.							
minimal					2	4	2
moderate					1		1
Total observations per lesion					3	4	3
HYPERPLASIA, ERYTHROCYTIC.							
mild							3
Total observations per lesion							3
BRAIN		(19)				(19)	(19)
NO ABNORMALITY DETECTED		19				19	19
FEMUR/KNEE JOINT		(19)				(19)	(19)
NO ABNORMALITY DETECTED		19				19	19
STERNUM		(19)				(19)	(19)
NO ABNORMALITY DETECTED		19				19	19

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
Table excludes 3 mice that were euthanized on test days 5 (mice 117 or 1112) and 9 (mouse 906).

Table 16
Incidence and Lesion Grades of Microscopic Observations in Male Mice (Continued)

LESIONS	TREATMENT per day	LESION INCIDENCE (NUMERIC) 0 mg/kg I	0.3 mg/kg III	1 mg/kg V	10 mg/kg VII	30 mg/kg IX	30/0 mg/kg Recovery XI
PENIS						(1)	
EROSION/ULCER.							
moderate						1	
Total observations per lesion						1	
PREPUTIAL GLANDS						(1)	
ECTASIA.							
mild						1	
Total observations per lesion						1	
SKIN					(1)		
ABSCESS.							
moderate					1		
Total observations per lesion					1		

Figures in parentheses are the number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified
Table excludes 3 mice that were euthanized on test days 5 (mice 117 or 1112) and 9 (mouse 906).

Table 17
Summary of Total Cell Counts

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
Final Body Weight (g)	33.02 1.33(19)	33.41 2.47(20)	33.77 1.81(20)	28.42 2.04(20)	25.99 2.84(19)	30.49 3.66(19)
SPLEEN						
Absolute Weight (g)	0.117 0.015(19)	0.116 0.032(20)	0.104 0.016(20)	0.066 0.019(20)	0.052 0.023(19)	0.076 0.022(19)
Weight Ratio (% Body Weight)	0.3553 0.0448(19)	0.3457 0.0824(20)	0.3066 0.0426(20)	0.2317 0.0623(20)	0.1949 0.0671(19)	0.2491 0.0578(19)
Half Weight (g)	0.058 0.008(19)	0.055 0.016(20)	0.051 0.009(20)	0.031 0.011(20)	0.026 0.010(19)	0.038 0.009(19)
Cell Suspension Volume (mL)	5.3 0.3(19)	5.5 0.3(20)	5.4 0.3(20)	5.4 0.2(20)	5.4 0.2(19)	5.5 0.2(19)
Number of Cells in Half (x 10^6 cells/mL)	12.18 4.05(18)	11.27 4.79(20)	12.20 2.41(20)	5.92 2.35(20)	4.36 2.70(19)	6.45 2.88(18)
Total Number of Cells (x 10^8)	1.29 0.34(18)	1.30 0.52(20)	1.34 0.25(20)	0.69* 0.25(20)	0.48* 0.35(19)	0.72* 0.34(18)

Table 17
Summary of Total Cell Counts (Continued)

	Group I 0 mg/kg	Group III 0.3 mg/kg	Group V 1 mg/kg	Group VII 10 mg/kg	Group IX 30 mg/kg	Group XI 30/0 mg/kg (Recovery)
THYMUS						
Absolute Weight (g)	0.050 0.010(19)	0.045 0.010(20)	0.049 0.012(20)	0.025 0.009(20)	0.025 0.013(19)	0.027 0.010(19)
Weight Ratio (% Body Weight)	0.1532 0.0337(19)	0.1369 0.0339(20)	0.1439 0.0351(20)	0.0872 0.0309(20)	0.0942 0.0477(19)	0.0881 0.0266(19)
Half Weight (g)	0.025 0.006(19)	0.022 0.006(20)	0.024 0.008(20)	0.012 0.005(20)	0.010 0.005(19)	0.014 0.005(19)
Cell Suspension Volume (mL)	5.5 0.2(19)	5.4 0.2(20)	5.5 0.2(20)	5.5 0.2(20)	5.4 0.2(19)	5.4 0.2(19)
Number of Cells in Half (x 10^6 cells/mL)	5.26 2.27(19)	5.36 2.14(20)	6.74 3.81(20)	2.18 2.36(20)	0.87 1.41(19)	1.05 1.37(18)
Total Number of Cells (x 10^8)	0.57 0.22(19)	0.60 0.24(20)	0.75 0.38(20)	0.25@ 0.27(20)	0.10@ 0.16(19)	0.28@ 0.79(18)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

NOTE: All data from groups III, V, VII, IX and XI were compared with the control (I) group data. In addition, data from group IX were compared with data from group XI; no significant differences between IX and XI were detected.

FIGURES

Figure 1
Representative Analytical Calibration Curve

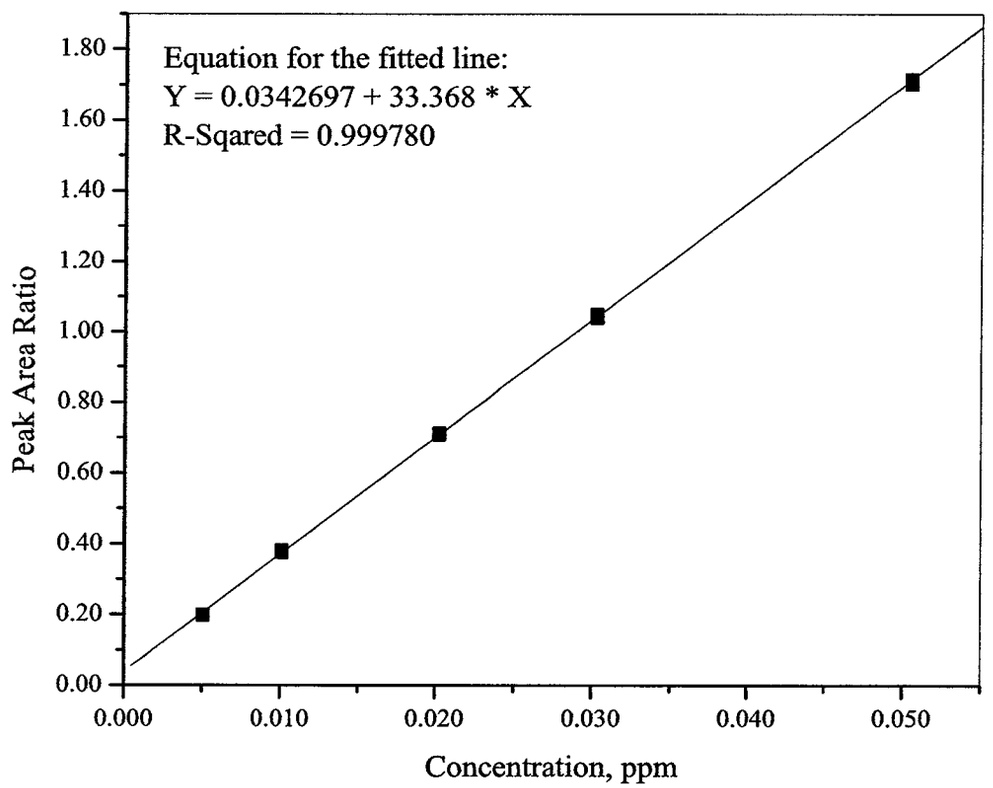


Figure 1: Calibration curve showing linear fit (line) to replicate peak area ratio measurements (squares) for matrix matched calibration solutions of APFO diluted over a concentration range of 0.00505 to 0.0505 ppm.

Figure 2
Representative LC/MS/MS Chromatograms

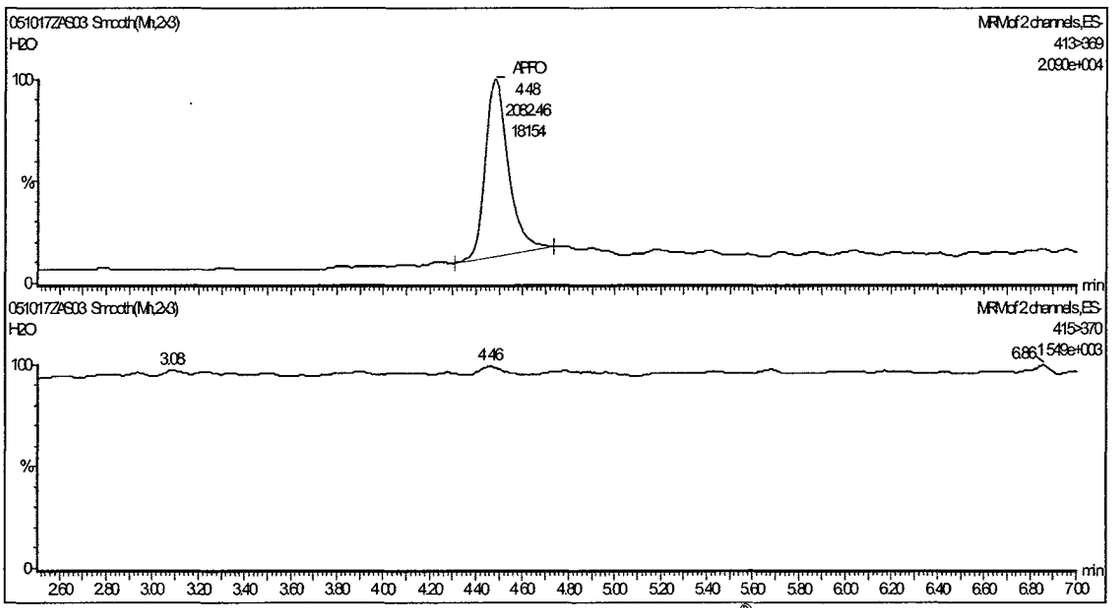


Figure 2a: Representative LC/MS/MS chromatogram of NANOpure® water used as the diluent in the study. Retention time for PFOA is approximately 4.5 minutes.

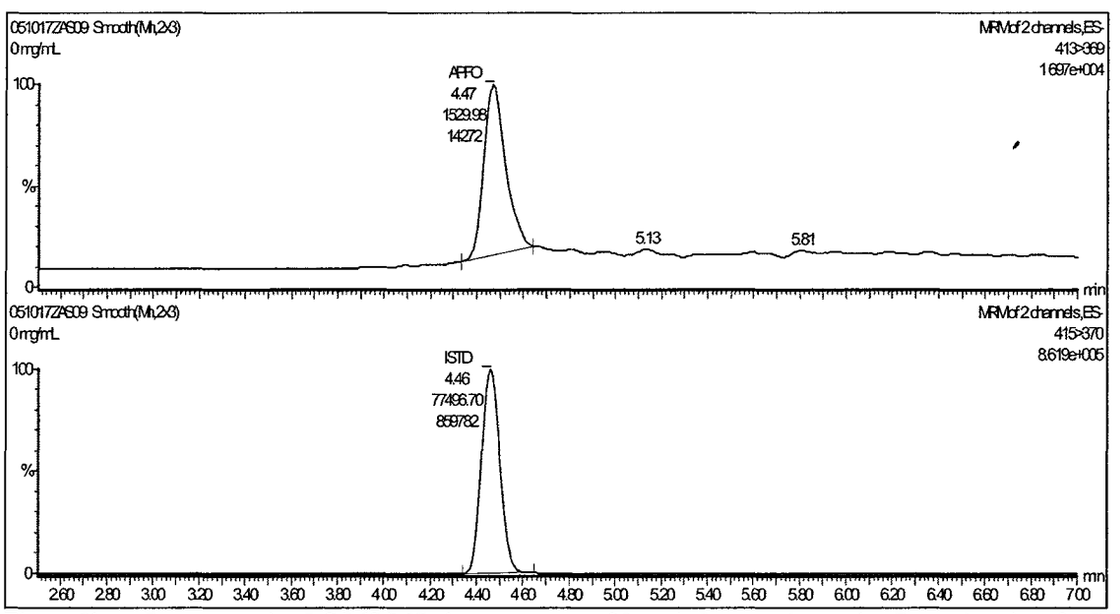


Figure 2b: Representative LC/MS/MS chromatogram of 0 mg/mL control sample. Retention time for PFOA is approximately 4.5 minutes.

Figure 2
Representative LC/MS/MS Chromatograms (Continued)

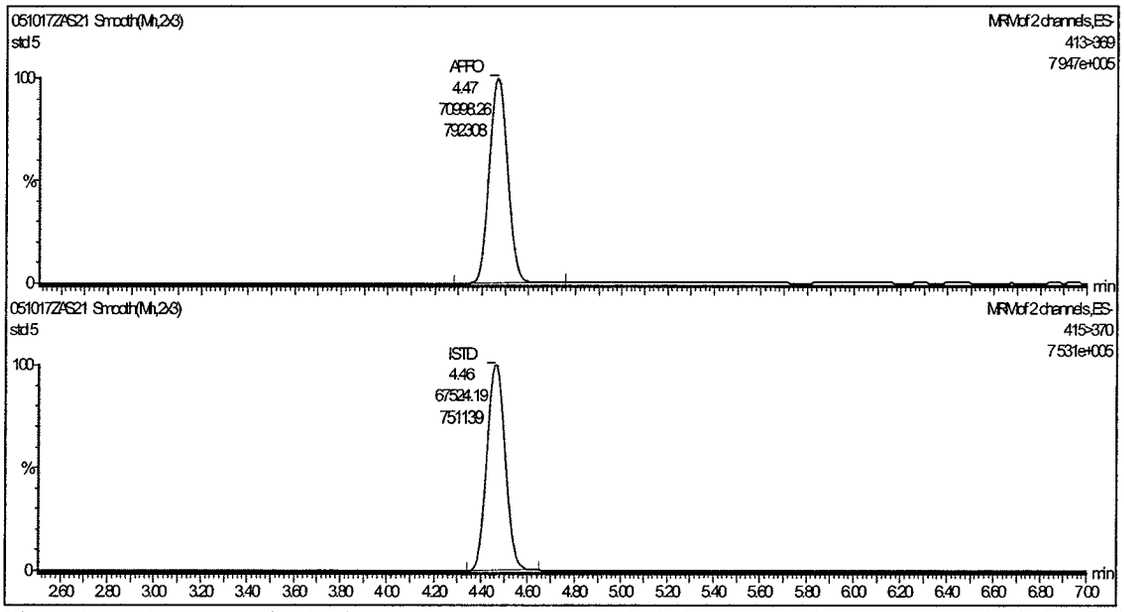


Figure 2c: Representative LC/MS/MS chromatogram of 0.0303 ppm APFO analytical standard (H22703-376) diluted with NANOpure® water after matrix correction.

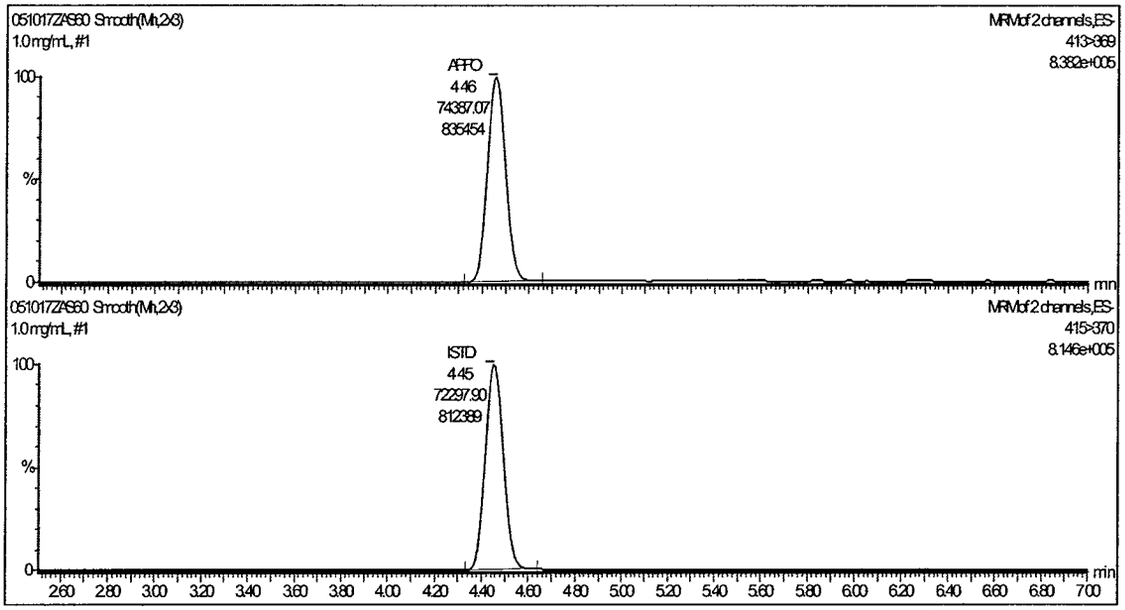


Figure 2d: Representative LC/MS/MS chromatogram of 1 mg/mL APFO dosing solution diluted to a nominal concentration of 0.03 mg/mL. The measured concentration of the representative solution is 0.979 mg/mL.

Figure 2
Representative LC/MS/MS Chromatograms (Continued)

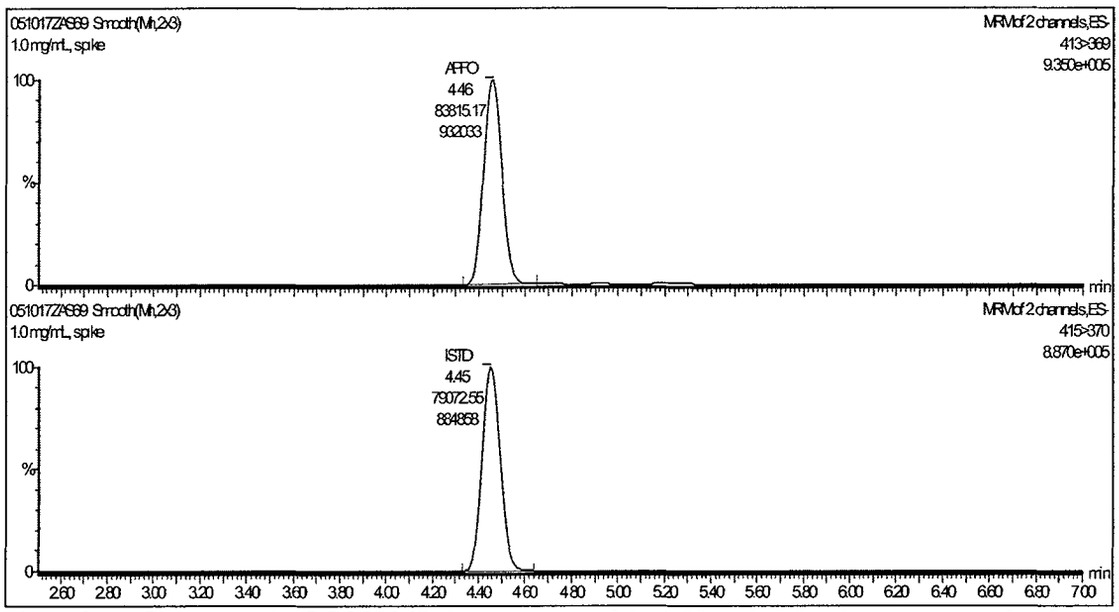
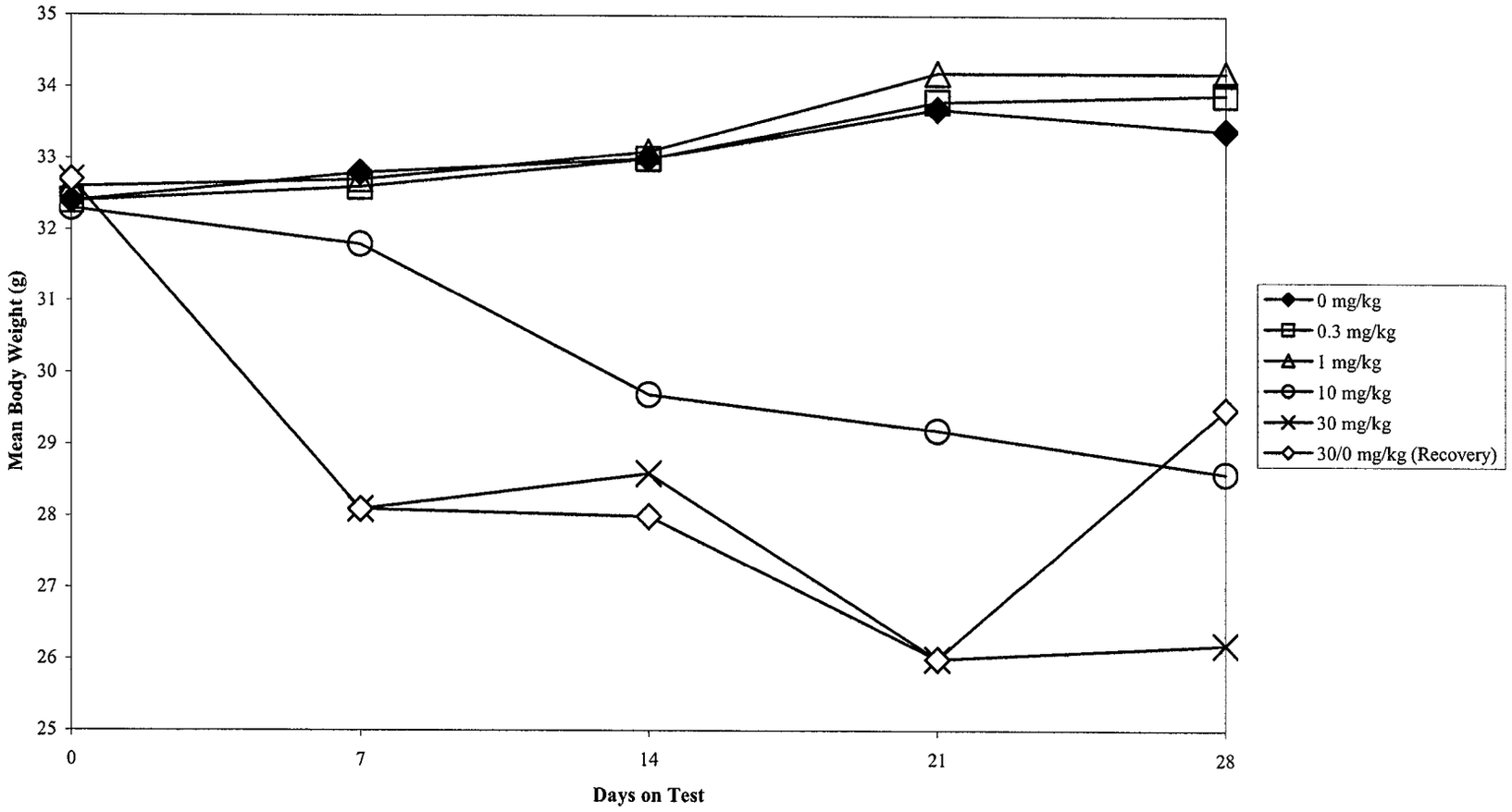


Figure 2e: Representative LC/MS/MS chromatogram of the 1.00 mg/mL level recovery sample of APFO diluted with NANOpure® water after matrix correction to a nominal concentration of 0.0300 ppm. The measured concentration of the representative recovery sample is 1.02 mg/mL.

Figure 3
Mean Body Weights of Male Mice



APPENDICES

Appendix A
Certificate of Analysis

Exygen RESEARCH
Precise Research. Proven Results.
3058 Research Drive
State College, PA 16801
T: 814.272.1039
exygen.com

Certificate of Analysis

CERTIFICATE OF ANALYSIS

This Certificate of Analysis fulfills the requirement for characterization of a test substance prior to a study subject to the GLP regulations. It documents the purity of the test substance. This work was conducted under TSCA Good Laboratory Practice Standards (40 CFR 792) and FIFRA Good Laboratory Practice Standards (40 CFR 160).

Designation of the Certified Material:
Compound: APFO (Linear)
Haskell Number: H27308

Analytical Data:
The Purity of the Certified Material was Established by LC/MS/MS

Purity: 19.5%

Last Date of Analysis: 07-November-2005
Re-certification Date: 07-November-2006

Origin of Certified Material:
E.I. du Pont de Nemours and Company
Wilmington, DE 19898
USA

Testing Facility/Performing Laboratory:
Exygen Research
3058 Research Drive
State College, PA 16801

Prepared By: _____ 11/15/05
Charles Simons Date
Study Director, Exygen Research

Facility Management: _____ for 15-Nov-05
John Flaherty John Flaherty Date
Vice-President, Exygen Research

Appendix B
Individual Body Weights

INDIVIDUAL BODY WEIGHTS

EXPLANATORY NOTES

ABBREVIATIONS:

g - grams

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 2	Body Weight g Day 3	Body Weight g Day 4	Body Weight g Day 5	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9
Male, I 0 mg/kg									
101	32.4		32.1	31.7	32.0	32.2	31.8	31.8	31.6
102	34.3		34.3	34.1	34.8	34.4	34.0	34.8	34.7
103	32.4		33.0	32.4	32.5	33.0	32.7	32.8	32.5
104	31.1		31.7	31.4	32.1	31.3	31.6	30.5	31.0
105	33.3		33.0	33.2	33.5	33.2	33.7	32.4	32.7
106	28.8		29.0	29.1	29.6	29.5	29.3	29.7	29.6
107	30.9		31.0	30.8	30.8	30.7	31.2	31.0	30.4
108	32.4		31.6	31.5	31.9	32.0	31.4	31.4	31.5
109	34.4		33.8	34.3	34.6	34.0	34.1	33.9	34.4
110	33.1		33.7	33.7	34.3	34.4	34.3	34.0	34.3
111	35.1	34.0	33.4	34.7	34.6	33.6	34.6	35.1	34.9
112	32.2	31.4	31.8	32.6	33.2	32.5	33.1	32.0	31.8
113	34.0	33.9	34.2	35.4	35.3	35.1	34.6	34.3	33.5
114	32.4	32.9	32.8	33.4	33.4	33.0	32.8	32.2	31.1
115	32.0	30.3	30.5	30.7	31.5	30.9	30.6	30.5	29.5
116	31.7	31.6	31.5	32.2	32.5	32.8	32.5	32.2	31.8
117	29.4	29.8	26.3	24.6	24.2				
118	33.3	33.4	33.4	34.4	35.0	34.3	34.0	33.1	33.5
119	30.8	30.5	30.5	31.6	32.0	32.1	31.6	31.8	31.8
120	34.2	34.1	34.2	35.6	35.5	35.9	34.8	35.3	34.5

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 2	Body Weight g Day 3	Body Weight g Day 4	Body Weight g Day 5	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9
Male, III 0.3 mg/kg									
301	32.6		33.0	32.9	33.5	33.8	33.5	33.4	33.0
302	34.8		34.7	34.7	35.6	35.1	34.4	34.2	34.6
303	33.9		34.6	34.9	35.5	34.9	35.3	35.3	35.2
304	32.4		33.5	33.6	34.0	34.2	34.0	33.9	33.7
305	32.2		33.4	33.1	33.4	33.3	33.1	32.6	32.7
306	30.9		31.2	30.8	31.5	32.0	31.6	32.2	31.6
307	30.5		30.0	30.1	30.9	30.3	29.9	29.7	29.8
308	31.6		32.1	32.7	33.3	33.0	31.8	32.0	32.2
309	32.9		32.1	31.8	32.4	32.4	31.5	31.3	31.4
310	33.4		33.8	33.5	34.4	34.1	33.5	32.9	32.9
311	35.6	36.1	36.1	36.6	36.4	36.6	36.4	36.2	36.1
312	30.7	31.2	31.5	31.9	32.3	31.8	31.9	31.7	31.5
313	33.5	32.8	32.8	32.8	33.0	33.2	32.6	32.8	32.5
314	30.8	31.1	31.2	31.7	31.7	31.2	32.1	30.7	31.0
315	34.0	33.4	33.4	33.8	34.6	34.2	33.8	34.2	33.7
316	32.7	32.3	32.1	32.8	33.2	33.3	32.9	32.6	33.2
317	29.0	29.8	29.5	30.1	30.1	30.3	29.8	29.7	29.2
318	32.2	31.2	31.0	31.2	31.1	31.0	30.4	30.3	30.2
319	29.4	29.7	29.5	29.8	30.1	30.1	30.1	29.9	29.8
320	34.1	33.4	33.7	34.8	34.4	34.7	34.4	34.1	33.8

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 2	Body Weight g Day 3	Body Weight g Day 4	Body Weight g Day 5	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9
Male, V 1 mg/kg									
501	32.8		33.3	33.3	34.3	34.0	33.9	34.4	33.9
502	34.6		34.6	34.6	35.9	35.0	35.1	34.3	33.8
503	33.8		34.0	33.6	34.1	33.8	33.6	33.6	33.8
504	31.4		31.1	31.3	31.8	31.5	31.4	31.9	30.8
505	32.6		32.9	32.1	32.8	32.5	32.0	31.7	32.1
506	28.6		29.5	29.7	30.2	30.4	30.5	30.5	30.4
507	31.0		30.9	31.0	31.5	31.6	31.4	31.2	30.8
508	32.5		33.1	32.8	33.7	33.6	33.5	33.6	33.5
509	32.9		32.6	32.9	33.6	33.5	33.3	32.4	32.9
510	32.9		32.1	32.3	33.3	32.2	31.6	31.4	31.1
511	36.1	35.2	35.4	36.0	36.5	36.1	35.5	35.6	35.6
512	32.5	31.4	31.8	32.5	32.4	32.4	31.9	31.2	31.9
513	35.1	33.4	33.4	34.5	34.8	35.4	34.7	34.2	33.8
514	31.8	31.6	31.5	32.1	32.2	31.9	31.6	31.6	31.3
515	34.3	33.2	33.6	34.8	35.0	35.2	34.5	35.2	34.5
516	31.6	30.9	31.1	32.4	32.3	32.8	32.1	32.1	31.6
517	29.6	28.7	29.0	29.4	29.7	29.8	29.7	29.7	29.3
518	31.8	31.2	31.9	32.8	32.8	33.2	33.0	32.5	32.4
519	32.4	30.7	27.5	28.6	29.0	29.7	29.5	28.8	28.6
520	34.1	33.6	33.6	34.5	34.9	35.0	34.3	34.0	34.4

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 2	Body Weight g Day 3	Body Weight g Day 4	Body Weight g Day 5	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9
Male, VII 10 mg/kg									
701	33.7		34.3	34.6	34.2	33.4	33.6	33.0	33.0
702	34.5		35.5	35.2	35.6	34.6	33.3	32.7	31.9
703	31.9		32.0	32.9	32.2	31.6	32.0	32.0	31.0
704	32.2		32.9	33.2	34.5	33.7	34.4	32.9	31.9
705	32.7		32.5	33.3	33.3	33.1	33.4	32.9	32.5
706	29.2		29.9	30.7	31.0	30.8	30.3	29.9	29.1
707	31.2		31.5	31.1	31.0	30.2	28.6	28.7	26.8
708	32.8		33.1	33.2	33.7	32.8	33.0	31.7	32.3
709	34.2		35.0	35.2	35.4	35.1	34.7	33.5	32.9
710	30.8		32.1	32.3	32.7	31.8	31.2	31.2	30.4
711	35.0	33.7	33.8	34.4	34.0	32.8	32.1	31.4	31.0
712	31.5	30.5	30.4	31.2	30.7	30.3	29.7	29.2	29.6
713	35.7	35.1	36.3	37.4	37.8	37.2	36.8	36.2	36.4
714	32.1	31.3	31.5	28.9	28.7	27.4	27.4	27.3	27.8
715	32.1	32.3	32.3	33.2	33.0	32.1	31.9	31.9	30.1
716	31.5	31.2	31.2	32.7	32.0	29.9	30.4	30.4	28.2
717	29.5	29.2	29.1	30.3	30.2	29.5	28.9	28.4	27.7
718	31.8	31.8	32.9	33.4	33.0	32.7	31.6	31.6	31.6
719	31.3	31.2	31.5	32.8	32.1	30.5	30.4	30.2	29.8
720	33.0	32.9	33.1	34.5	33.7	33.0	32.3	30.6	31.5

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 2	Body Weight g Day 3	Body Weight g Day 4	Body Weight g Day 5	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9
Male, IX 30 mg/kg									
901	33.7		33.5	31.4	30.5	28.4	25.5	23.0	23.6
902	35.9		36.3	33.8	32.3	30.1	27.4	26.1	25.0
903	32.3		32.1	30.8	29.8	28.8	28.4	27.7	27.2
904	31.2		30.1	27.6	28.6	24.4	22.6	24.1	25.3
905	33.4		34.5	32.5	29.3	26.5	24.2	23.7	24.7
906	29.4		30.1	29.1	28.8	26.1	24.6	23.4	21.9
907	30.4		30.1	29.0	27.7	26.3	24.4	23.0	22.4
908	31.2		32.6	30.6	30.0	27.3	25.7	25.9	26.4
909	34.2		34.9	33.6	32.5	30.7	28.5	26.5	26.4
910	33.7		34.4	33.4	32.0	28.4	26.2	24.8	24.8
911	37.5	38.9	38.6	37.9	35.5	33.5	30.2	30.0	30.1
912	33.1	33.0	31.6	32.6	31.0	30.3	29.5	28.6	27.8
913	33.4	33.2	33.3	33.3	33.1	31.7	31.5	31.5	30.7
914	31.3	31.2	32.1	33.1	32.5	31.1	30.9	29.9	29.3
915	34.7	35.8	36.0	35.9	35.1	34.5	32.9	33.6	32.4
916	31.2	31.6	31.8	30.7	29.9	29.2	27.8	29.8	28.3
917	28.7	29.8	29.3	29.4	30.0	30.1	28.9	29.5	29.2
918	32.4	32.8	33.3	32.8	32.3	31.2	29.9	29.8	29.9
919	31.1	31.7	31.8	31.5	30.9	30.2	29.0	29.1	29.0
920	35.1	35.2	35.9	36.5	35.7	35.0	34.3	35.1	34.0

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 2	Body Weight g Day 3	Body Weight g Day 4	Body Weight g Day 5	Body Weight g Day 6	Body Weight g Day 7	Body Weight g Day 8	Body Weight g Day 9
Male, XI 30/0 mg/kg (Recovery)									
1101	32.4		33.1	32.0	32.5	30.0	30.2	30.2	29.4
1102	36.0		36.9	35.8	35.9	35.6	34.5	35.8	35.4
1103	32.7		34.7	33.9	33.9	33.0	33.6	33.5	33.5
1104	33.1		33.6	33.3	32.6	30.8	29.6	29.5	29.2
1105	33.0		34.6	32.8	31.6	28.6	27.6	27.3	29.7
1106	30.1		31.4	29.7	28.1	26.2	24.8	26.7	27.1
1107	30.4		31.1	29.8	29.9	26.9	25.5	25.8	25.7
1108	32.6		33.7	32.0	31.8	29.3	26.8	24.7	22.6
1109	34.4		36.1	33.3	32.2	29.7	27.3	27.1	25.8
1110	31.4		33.2	31.9	30.9	30.9	29.9	31.9	31.9
1111	36.6	35.6	35.5	36.0	34.3	32.9	30.6	30.5	30.3
1112	31.4	31.7	29.8	28.4	27.5				
1113	33.3	33.5	34.4	33.1	32.7	30.8	30.2	32.8	32.3
1114	31.7	32.4	32.1	32.2	31.9	30.8	28.6	28.5	26.5
1115	32.3	32.1	31.5	31.4	30.6	30.7	29.4	30.4	29.5
1116	32.5	31.8	31.2	30.6	28.0	25.0	23.4	24.6	24.9
1117	32.2	31.6	30.9	30.7	29.0	25.9	23.4	21.3	20.8
1118	32.5	32.8	32.4	31.6	31.4	29.0	28.1	29.0	29.3
1119	31.6	32.1	29.8	28.1	26.3	24.1	24.7	25.4	24.3
1120	33.4	33.2	33.6	33.9	29.4	27.9	25.2	23.9	24.8

Individual Body Weights

	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18
Male, I 0 mg/kg									
101	31.4	30.8	30.8	30.3	30.9	30.7	30.1	30.7	31.1
102	34.5	34.6	34.7	34.6	35.0	34.2	34.4	34.7	34.6
103	32.5	32.3	32.5	32.7	33.0	33.5	32.9	33.1	33.9
104	31.0	31.2	31.7	32.0	32.6	31.8	32.0	32.8	33.2
105	32.8	33.4	33.7	34.2	34.0	34.2	33.1	34.1	34.1
106	29.7	29.6	29.2	30.0	29.9	29.8	29.7	30.2	30.4
107	30.5	30.9	31.1	31.0	31.3	31.4	30.7	31.6	31.6
108	31.6	31.9	31.1	31.3	31.3	31.7	31.0	31.9	31.4
109	34.1	34.0	34.7	34.3	34.0	34.2	33.4	34.4	34.4
110	34.4	33.8	34.0	33.7	33.9	34.1	33.8	34.4	34.4
111	34.3	35.6	35.8	36.1	37.0	34.7	35.7	36.4	36.0
112	32.2	32.5	32.5	32.6	32.7	32.3	32.3	33.1	33.4
113	34.1	34.1	33.7	33.6	34.1	33.5	34.1	33.9	34.4
114	31.2	31.9	31.7	32.2	32.0	32.2	32.4	32.2	32.7
115	30.1	30.3	30.6	30.5	30.8	30.3	30.8	31.0	32.1
116	31.8	32.2	32.4	32.2	32.6	32.8	32.9	33.2	33.5
117									
118	33.6	33.8	33.5	33.6	34.4	34.3	34.7	34.6	35.2
119	31.8	32.5	32.6	32.5	33.1	32.4	32.8	32.9	33.2
120	35.1	36.0	35.6	34.3	34.9	35.2	35.4	35.7	35.7

Individual Body Weights

	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18
Male, III 0.3 mg/kg									
301	33.2	33.3	33.6	33.7	33.8	33.8	34.0	34.3	34.3
302	34.5	34.6	34.5	35.2	35.0	35.0	34.1	35.1	35.3
303	35.6	35.7	35.4	35.9	35.8	35.7	36.1	36.7	36.7
304	34.1	34.0	34.8	34.6	34.6	34.8	34.2	34.9	35.1
305	32.9	32.8	33.3	33.4	33.2	33.5	32.9	34.0	33.9
306	31.8	31.8	32.0	32.6	32.6	32.5	32.3	33.0	33.0
307	29.9	30.3	30.2	30.1	30.5	30.5	29.8	30.7	30.5
308	32.8	32.2	33.0	32.2	33.0	33.7	32.6	33.8	33.1
309	31.5	31.8	31.8	31.5	31.0	31.6	30.8	31.6	31.7
310	33.5	33.3	33.8	34.0	33.9	34.3	34.0	34.4	34.1
311	35.9	36.1	36.0	35.9	36.0	35.9	36.6	37.1	36.8
312	31.6	31.8	32.0	31.9	31.9	31.6	32.7	32.6	32.8
313	33.2	33.6	34.1	33.4	33.6	33.3	33.5	33.4	33.7
314	31.5	32.2	32.0	31.8	32.9	32.2	32.8	32.4	33.1
315	33.6	34.1	33.6	33.7	34.0	33.4	33.7	33.9	34.2
316	32.7	33.4	33.0	32.9	32.3	31.7	32.1	32.3	32.0
317	30.1	30.5	30.2	30.2	29.9	30.2	30.3	30.3	30.7
318	30.3	30.5	30.3	30.7	30.1	29.6	30.4	30.0	29.8
319	29.8	30.2	30.5	30.0	30.3	29.7	30.4	29.7	30.7
320	33.4	34.5	34.7	35.0	35.3	35.4	36.4	36.4	36.5

Individual Body Weights

	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18
Male, V 1 mg/kg									
501	33.8	34.1	34.3	33.8	34.5	34.7	34.2	34.8	34.8
502	33.6	33.7	33.4	33.8	34.4	34.1	33.5	33.9	34.0
503	34.3	34.4	34.2	34.6	34.9	35.0	34.4	35.1	34.7
504	31.1	31.4	31.2	31.6	31.3	31.9	31.2	32.4	32.7
505	31.9	32.5	32.3	32.7	32.5	32.4	32.3	32.9	33.2
506	30.8	31.4	31.7	31.5	31.9	32.6	32.5	33.3	33.7
507	31.0	31.0	31.1	30.8	30.7	31.2	30.9	31.4	31.3
508	33.6	33.9	33.4	34.0	34.2	34.5	33.9	34.6	34.8
509	32.6	33.0	33.2	33.3	33.2	33.8	33.6	34.0	34.8
510	30.6	30.2	30.5	30.4	30.6	31.1	31.0	31.9	31.8
511	35.2	35.5	35.4	35.4	35.3	34.7	35.4	35.7	35.5
512	32.0	32.1	32.3	32.5	32.9	32.8	33.2	33.4	33.9
513	34.4	35.2	34.7	35.0	35.4	34.6	34.7	35.6	35.9
514	31.5	31.7	32.2	31.7	32.0	31.3	32.0	32.2	32.4
515	34.8	35.3	35.1	35.0	35.9	35.2	35.9	36.5	36.8
516	31.6	31.9	32.1	32.2	32.2	31.7	32.3	33.5	33.5
517	29.6	30.0	30.2	30.0	30.3	30.7	30.9	31.3	31.4
518	33.0	33.3	33.3	33.3	33.4	33.2	34.0	34.2	35.2
519	28.5	28.5	29.1	29.3	29.3	28.6	29.3	29.5	30.2
520	34.5	34.8	35.2	35.5	36.1	34.9	35.6	35.8	36.3

Individual Body Weights

	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18
Male, VII 10 mg/kg									
701	32.4	32.7	31.1	31.2	32.0	31.8	31.6	31.9	32.1
702	32.8	31.8	32.5	32.4	32.2	32.5	31.7	32.8	32.3
703	30.9	31.4	30.9	31.4	30.2	31.1	29.7	29.8	30.3
704	31.4	31.2	31.0	29.6	29.1	28.6	28.3	29.4	29.0
705	32.4	30.5	30.7	32.1	30.7	31.2	31.3	30.3	30.8
706	28.9	27.2	27.0	28.3	28.3	28.2	28.1	27.9	27.8
707	26.1	25.4	24.8	25.1	24.1	24.9	25.4	25.1	25.0
708	33.7	31.7	31.6	32.0	31.4	31.1	30.7	30.8	30.6
709	32.8	31.7	31.3	31.9	32.6	32.3	30.5	30.4	30.7
710	30.0	29.6	30.2	29.4	29.5	30.2	29.6	29.1	29.3
711	30.2	29.5	29.1	28.7	28.8	28.5	27.6	27.3	27.1
712	29.6	30.0	29.0	29.8	29.3	29.1	29.4	29.3	29.9
713	35.7	35.6	34.4	34.6	34.4	33.4	33.2	33.2	32.2
714	28.0	28.9	29.0	30.1	29.0	29.5	29.8	30.0	29.1
715	30.4	29.9	29.1	28.9	28.8	29.4	29.4	28.9	29.4
716	28.2	29.8	28.5	27.5	26.9	28.1	26.3	26.9	29.1
717	27.2	27.1	27.9	27.1	26.8	26.8	26.9	26.9	26.8
718	32.1	32.1	30.7	31.1	31.1	30.5	30.8	30.6	33.5
719	30.0	29.5	29.2	30.2	29.9	29.1	29.5	30.9	30.3
720	30.0	31.3	29.3	29.0	28.2	27.9	28.1	27.0	27.8

Individual Body Weights

	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18
Male, IX 30 mg/kg									
901	25.4	29.8	31.8	32.4	32.5	31.3	29.8	28.9	26.7
902	25.8	28.5	30.5	31.4	31.9	30.5	27.8	26.5	24.8
903	26.9	26.5	25.9	25.2	25.2	24.7	25.4	25.1	24.9
904	26.5	26.5	26.4	26.1	25.8	26.4	25.1	25.4	24.9
905	27.5	28.1	28.9	29.3	29.3	28.1	26.8	28.0	25.8
906									
907	21.9	21.2	21.6	22.3	23.0	22.9	23.4	23.5	23.5
908	27.2	26.0	26.2	26.4	25.5	26.5	25.2	26.0	25.9
909	28.1	28.9	29.1	29.3	29.1	28.2	26.9	25.6	25.0
910	25.2	25.0	28.1	29.6	29.4	30.1	28.9	28.4	26.2
911	29.8	29.8	29.3	28.6	27.8	28.1	28.1	28.4	27.1
912	27.1	26.5	25.5	25.3	25.0	24.8	24.6	24.3	24.0
913	30.7	30.6	30.9	29.5	29.2	28.9	29.0	28.8	28.8
914	29.6	30.2	30.1	29.8	29.6	29.6	29.4	28.8	29.2
915	31.7	32.3	31.9	32.1	32.4	32.6	33.2	32.5	33.0
916	27.5	28.0	27.9	27.0	25.9	26.6	26.5	25.9	25.2
917	29.3	29.4	28.6	28.7	29.4	29.0	29.9	29.7	30.3
918	29.2	29.5	29.1	28.9	28.8	28.2	28.2	28.5	28.8
919	29.4	29.3	29.9	28.9	29.3	28.5	28.7	28.2	28.0
920	32.6	33.2	34.1	34.1	33.4	33.5	33.1	32.3	31.5

Individual Body Weights

	Body Weight g Day 10	Body Weight g Day 11	Body Weight g Day 12	Body Weight g Day 13	Body Weight g Day 14	Body Weight g Day 15	Body Weight g Day 16	Body Weight g Day 17	Body Weight g Day 18
Male, XI 30/0 mg/kg (Recovery)									
1101	30.1	28.8	28.4	28.5	28.1	29.0	27.2	27.6	27.1
1102	35.1	33.4	33.0	31.7	30.9	32.6	31.2	32.1	31.6
1103	32.2	31.7	31.2	29.9	29.3	29.6	28.4	27.7	27.3
1104	28.7	29.1	29.6	29.5	29.0	29.4	27.8	27.9	27.9
1105	31.1	31.1	31.7	32.4	32.0	30.8	30.4	29.5	29.9
1106	27.4	24.9	26.0	26.8	26.0	26.3	25.9	27.5	27.6
1107	24.4	25.2	24.6	24.3	23.9	24.8	24.2	23.6	23.0
1108	22.0	22.3	24.8	27.4	28.8	30.4	28.7	28.6	26.4
1109	25.9	27.0	33.2	33.9	34.2	33.2	29.2	26.6	24.2
1110	30.8	31.3	28.6	27.2	27.6	28.0	27.0	29.1	30.2
1111	30.4	30.5	30.3	29.7	29.4	29.7	29.5	29.4	29.4
1112									
1113	31.8	31.4	31.4	30.0	29.4	28.7	28.9	29.5	30.3
1114	28.3	27.9	27.1	27.0	27.4	26.8	27.7	26.8	26.5
1115	28.8	29.0	28.9	28.9	28.4	28.2	28.5	29.6	29.3
1116	24.0	24.9	24.6	24.0	23.2	24.6	23.8	23.5	23.4
1117	21.6	23.8	25.7	27.3	28.0	25.4	26.5	24.8	25.0
1118	28.1	28.1	27.2	26.9	25.8	25.3	25.7	24.9	24.8
1119	24.7	25.8	24.1	23.9	25.2	23.8	21.9	22.7	23.2
1120	26.8	28.7	28.8	26.5	26.2	25.5	25.1	25.3	24.6

Individual Body Weights

	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27
Male, I 0 mg/kg									
101	31.0	31.2	31.2	31.1	31.5	31.1	31.2	31.4	31.4
102	35.1	34.9	35.2	35.0	35.1	34.9	35.6	35.8	36.4
103	34.4	34.3	34.1	33.7	33.4	34.0	34.5	33.8	33.9
104	33.3	33.4	33.4	32.2	32.0	32.5	32.7	32.4	33.3
105	34.4	34.0	34.4	33.6	33.6	34.5	34.2	33.5	33.8
106	31.0	30.8	30.7	31.2	31.5	31.0	31.4	31.4	31.1
107	32.2	31.7	32.1	32.4	31.7	32.3	32.4	32.7	33.4
108	32.1	31.9	31.8	32.2	31.8	31.5	31.5	31.1	31.2
109	35.3	34.8	34.3	34.3	34.2	33.9	33.9	34.3	33.8
110	35.0	34.7	34.7	34.9	34.5	34.4	34.6	34.6	35.2
111	36.5	36.4	35.7	35.6	35.4	34.5	35.5	35.6	34.5
112	32.9	33.6	33.7	33.4	33.5	33.7	33.9	34.2	34.4
113	33.9	34.2	34.4	33.6	34.5	34.5	34.4	34.5	34.2
114	32.1	32.9	33.7	33.4	33.6	33.7	34.2	33.6	33.7
115	31.2	32.0	32.0	32.1	31.9	31.7	32.6	32.4	31.3
116	33.5	34.0	34.3	33.9	34.1	33.7	33.8	33.4	33.7
117									
118	35.0	35.0	35.7	35.2	35.8	35.4	35.8	35.4	34.4
119	33.3	33.8	33.9	33.4	33.8	33.8	34.2	34.4	34.7
120	35.4	35.7	35.5	34.9	35.4	35.0	35.1	35.3	34.6

Individual Body Weights

	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27
Male, III 0.3 mg/kg									
301	34.8	34.8	35.0	35.2	35.0	35.4	36.3	36.0	36.4
302	36.2	35.6	35.8	36.3	36.3	36.4	36.9	35.9	36.7
303	37.0	36.4	36.6	36.7	36.6	36.3	37.3	37.2	37.6
304	35.8	35.6	35.7	36.1	36.3	36.4	37.1	37.5	37.7
305	34.6	34.3	34.6	34.1	35.4	35.0	35.1	35.6	36.0
306	33.7	33.3	33.2	33.5	33.8	33.2	33.9	33.7	33.4
307	30.8	30.7	31.1	31.3	31.4	31.1	31.5	31.4	31.5
308	34.0	34.3	33.9	34.1	34.0	34.7	35.1	34.7	35.1
309	31.8	31.5	32.2	31.7	31.7	31.6	31.5	31.6	31.6
310	34.4	34.2	34.5	33.7	34.4	34.8	34.9	35.1	35.1
311	36.6	37.0	37.5	36.9	37.2	36.7	37.2	37.3	37.5
312	32.4	33.1	33.3	32.7	33.2	33.3	33.8	33.5	33.8
313	33.3	33.3	33.8	33.9	33.8	34.0	32.9	32.7	32.9
314	32.7	32.9	32.9	32.6	32.4	32.5	33.1	33.1	32.9
315	33.6	34.0	34.5	33.7	34.3	34.5	35.1	34.1	34.9
316	31.4	32.0	32.4	31.5	32.2	32.5	32.7	32.2	31.9
317	30.3	30.9	31.1	30.3	30.3	29.9	30.1	30.1	30.3
318	29.9	30.0	30.8	30.2	30.8	30.9	31.3	31.1	31.2
319	30.2	30.8	31.0	30.9	31.1	30.8	31.5	31.2	31.4
320	35.8	36.5	36.4	37.1	36.8	37.0	37.5	37.2	36.8

Individual Body Weights

	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27
Male, V 1 mg/kg									
501	34.7	34.5	35.1	34.2	34.3	34.7	34.4	34.2	34.0
502	34.1	33.7	33.9	33.5	33.2	33.5	33.8	33.6	34.0
503	35.1	35.0	34.8	34.2	34.5	34.5	34.7	34.3	34.3
504	32.7	32.9	33.3	32.9	33.2	33.6	33.7	33.9	34.2
505	32.9	33.2	33.0	32.7	33.0	33.2	33.8	33.9	33.4
506	34.3	34.6	34.4	35.0	35.1	35.3	35.9	35.3	35.6
507	31.2	31.3	31.0	30.7	31.0	31.4	31.6	31.6	31.7
508	34.6	34.6	34.6	34.6	34.9	34.7	35.2	34.8	35.2
509	34.4	34.9	35.0	34.7	34.9	35.5	35.5	35.0	35.3
510	32.8	32.7	32.8	33.0	33.3	32.9	33.2	32.5	33.0
511	35.4	36.1	36.0	35.6	36.6	37.0	37.4	37.5	38.0
512	33.6	33.7	34.2	34.1	34.6	34.6	35.7	35.3	35.4
513	35.2	35.4	36.1	35.3	36.5	36.2	36.5	36.8	36.8
514	32.1	32.3	32.2	32.6	32.5	32.8	32.8	32.0	32.5
515	35.3	36.2	37.0	36.9	35.8	36.0	36.5	36.4	36.4
516	32.7	32.8	33.4	32.3	32.6	32.7	32.8	32.8	32.6
517	31.1	31.4	32.3	32.0	32.3	32.1	32.7	32.5	32.7
518	34.5	34.9	36.2	36.0	36.2	35.6	36.2	36.7	36.0
519	29.5	30.5	31.0	30.9	31.1	31.2	31.3	31.6	31.6
520	35.4	35.7	36.9	35.7	35.8	36.7	37.1	36.4	35.9

Individual Body Weights

	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27
Male, VII 10 mg/kg									
701	32.4	31.8	32.0	31.5	30.9	31.4	31.7	31.4	31.8
702	32.0	32.8	32.6	31.7	31.3	32.7	32.5	32.7	31.4
703	30.3	29.5	29.2	29.7	29.3	29.1	28.9	28.6	28.9
704	29.3	28.8	28.6	29.1	28.8	29.0	28.7	28.8	28.6
705	30.0	29.6	29.7	30.3	29.8	29.5	29.4	28.6	29.1
706	27.5	27.8	27.3	28.2	28.3	28.6	28.2	27.8	27.5
707	24.6	24.3	24.7	25.6	26.0	25.8	26.0	25.4	24.5
708	30.6	31.2	32.1	32.3	32.8	32.0	31.7	31.1	30.6
709	29.9	29.7	29.7	30.1	29.4	28.6	28.4	28.1	28.3
710	29.1	28.8	28.6	28.9	28.4	28.0	27.2	27.4	28.0
711	26.4	26.5	27.1	27.4	28.3	29.0	28.7	27.4	27.2
712	29.7	29.8	30.7	30.3	29.8	30.5	30.2	30.6	30.1
713	31.6	31.6	31.4	31.2	31.0	31.2	30.8	30.3	30.3
714	28.8	28.6	29.2	29.6	29.1	30.2	30.0	30.2	29.7
715	28.4	28.6	28.0	29.3	29.0	28.9	28.0	27.7	28.2
716	27.3	27.2	29.1	27.6	27.1	28.0	27.7	28.0	27.1
717	26.5	26.3	26.4	26.6	27.1	26.6	25.8	25.6	25.7
718	29.8	29.4	28.6	28.3	28.5	28.6	28.0	29.6	30.0
719	30.6	29.9	30.9	31.2	30.8	30.5	29.3	30.1	29.5
720	27.2	27.7	28.1	29.1	29.1	28.8	28.3	28.9	26.9

Individual Body Weights

	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27
Male, IX 30 mg/kg									
901	25.2	23.3	21.5	23.8	24.8	24.4	24.9	25.9	26.7
902	23.5	22.9	22.8	24.0	23.3	24.0	24.0	25.0	24.6
903	25.6	25.0	24.7	25.1	24.9	24.9	24.7	24.8	24.4
904	23.6	26.3	23.7	24.6	24.1	24.8	24.0	24.6	24.4
905	24.7	24.0	22.2	21.6	23.4	22.5	23.7	24.3	24.3
906									
907	23.7	23.7	23.6	23.6	23.5	23.4	23.1	22.4	21.9
908	25.6	25.5	25.7	26.6	26.3	26.3	26.3	26.5	25.7
909	25.2	24.4	24.0	25.2	26.7	26.3	26.1	25.6	25.3
910	25.8	26.0	24.7	25.1	25.9	26.4	26.9	28.1	28.4
911	27.0	27.7	27.8	29.5	29.8	29.5	28.4	27.8	26.4
912	23.8	23.6	22.7	23.2	23.6	22.6	22.3	22.1	22.0
913	28.6	28.6	28.5	29.4	29.3	28.9	28.6	28.4	28.2
914	30.0	28.8	28.2	29.9	29.3	29.1	28.2	28.7	27.8
915	32.1	32.5	33.0	33.4	32.9	32.6	32.5	33.1	32.5
916	24.9	24.8	25.0	25.6	25.5	25.3	24.7	24.8	24.0
917	29.8	29.8	30.1	30.3	29.9	29.7	29.4	29.8	30.4
918	27.9	28.1	28.5	28.4	27.9	28.1	28.1	28.0	28.5
919	27.8	28.1	28.2	27.5	27.3	27.0	26.9	26.6	26.9
920	30.3	29.5	28.7	28.4	28.2	28.9	29.3	29.0	28.9

Individual Body Weights

	Body Weight g Day 19	Body Weight g Day 20	Body Weight g Day 21	Body Weight g Day 22	Body Weight g Day 23	Body Weight g Day 24	Body Weight g Day 25	Body Weight g Day 26	Body Weight g Day 27
Male, XI 30/0 mg/kg (Recovery)									
1101	27.9	28.1	27.4	29.1	29.4	29.0	29.3	30.1	30.2
1102	32.6	32.9	32.6	33.1	33.8	32.7	34.0	34.2	36.8
1103	27.0	25.9	26.1	28.6	28.7	28.5	28.9	30.2	31.4
1104	27.1	27.7	26.0	26.4	28.1	27.6	27.3	27.9	28.7
1105	28.1	29.2	27.4	30.7	33.2	31.4	32.5	32.6	31.8
1106	27.5	27.0	25.9	25.7	26.2	25.4	25.6	25.5	25.7
1107	22.9	23.1	23.3	25.0	24.8	23.9	23.6	23.6	24.3
1108	24.8	24.2	23.6	23.4	23.3	23.6	25.2	26.0	28.4
1109	22.5	22.9	22.7	24.5	25.5	27.3	29.7	32.6	34.3
1110	29.8	28.4	26.0	23.4	22.3	22.3	22.6	23.4	24.6
1111	28.4	28.8	28.5	28.5	28.3	28.5	28.5	29.2	29.4
1112									
1113	31.1	30.8	30.7	31.3	31.1	30.4	30.3	31.2	32.2
1114	26.6	25.8	25.5	26.9	28.2	27.6	26.5	28.2	29.5
1115	28.9	28.9	29.2	29.2	29.3	29.3	29.1	29.9	29.7
1116	22.8	23.7	22.9	23.2	24.3	23.9	23.6	23.8	24.1
1117	24.0	23.9	23.6	23.8	23.6	25.0	23.6	26.0	25.4
1118	25.0	26.0	26.4	26.4	27.8	26.6	26.9	27.0	27.7
1119	21.4	22.8	22.4	23.2	23.6	23.3	24.5	24.2	23.9
1120	25.1	24.4	24.2	25.0	25.5	25.7	26.6	27.6	27.9

Individual Body Weights

	Body Weight g Day 28
Male, I 0 mg/kg	
101	31.3
102	35.8
103	34.4
104	33.6
105	33.7
106	30.9
107	32.3
108	30.7
109	33.1
110	34.4
111	34.0
112	34.0
113	34.5
114	33.6
115	31.2
116	33.4
117	
118	34.8
119	34.3
120	35.0

Individual Body Weights

	Body Weight g Day 28
Male, III 0.3 mg/kg	
301	35.7
302	36.0
303	37.6
304	38.0
305	35.2
306	33.1
307	31.1
308	33.8
309	31.4
310	34.7
311	37.5
312	34.0
313	32.5
314	32.4
315	34.6
316	31.8
317	30.0
318	31.0
319	31.0
320	36.7

Individual Body Weights

	Body Weight g Day 28
Male, V 1 mg/kg	
501	33.8
502	34.0
503	33.8
504	33.5
505	33.1
506	35.5
507	31.9
508	34.5
509	35.0
510	32.6
511	37.0
512	35.8
513	36.8
514	32.2
515	36.3
516	32.2
517	32.7
518	35.7
519	30.7
520	36.2

Individual Body Weights

	Body Weight g Day 28
Male, VII 10 mg/kg	
701	32.5
702	31.4
703	28.4
704	28.2
705	28.7
706	27.2
707	24.4
708	31.1
709	27.4
710	27.2
711	26.9
712	29.6
713	31.9
714	29.4
715	27.1
716	27.5
717	26.1
718	30.2
719	29.2
720	26.9

Individual Body Weights

	Body Weight g Day 28
Male, IX 30 mg/kg	
901	26.2
902	24.1
903	24.1
904	23.6
905	24.1
906	
907	21.5
908	25.0
909	24.5
910	28.9
911	26.2
912	22.1
913	28.2
914	27.9
915	33.2
916	23.5
917	29.7
918	28.9
919	27.9
920	29.0

Individual Body Weights

	Body Weight g Day 28
Male, XI 30/0 mg/kg (Recovery)	
1101	30.3
1102	36.9
1103	31.5
1104	29.3
1105	33.0
1106	26.2
1107	25.2
1108	29.9
1109	33.4
1110	26.0
1111	30.3
1112	
1113	33.8
1114	30.5
1115	30.7
1116	25.3
1117	26.7
1118	28.2
1119	24.8
1120	27.9

Appendix C
Individual Final Body and Liver Weights

INDIVIDUAL FINAL BODY AND LIVER WEIGHTS

EXPLANATORY NOTES

ABBREVIATIONS:

FBW	-	final body weight
na	-	not applicable
NW	-	not weighed
S.D.	-	standard deviation
WE	-	weighing error

FOOTNOTES:

a Animal was sacrificed *in extremis* prior to this analysis.

Individual Final Body and Liver Weights

Animal	FBW (g)	Liver (g)	FBW - Liver (g)
101	31.0	1.623	29.4
102	34.7	2.017	32.7
103	33.4	1.736	31.7
104	32.5	1.768	30.7
105	33.0	1.459	31.5
106	31.2	1.717	29.5
107	31.9	1.861	30.0
108	30.3	1.727	28.6
109	32.7	1.711	31.0
110	33.9	1.634	32.3
111	32.6	1.801	30.8
112	33.9	WE	na
113	34.6	WE	na
114	33.7	2.064	31.6
115	31.5	1.718	29.8
116	34.2	1.795	32.4
117	[a]	na	na
118	34.5	2.172	32.3
119	34.3	1.859	32.4
120	33.5	1.639	31.9
MEAN	**33.0**	**1.782**	**31.1**
S.D.	**1.33**	**0.18**	**1.26**
301	35.1	2.609	32.5
302	36.1	2.405	33.7
303	37.4	2.512	34.9
304	37.2	2.758	34.4
305	34.5	2.520	32.0
306	33.1	2.539	30.6
307	31.3	2.036	29.3
308	33.7	2.372	31.3
309	29.9	1.988	27.9
310	32.8	2.492	30.3
311	36.6	2.896	33.7
312	33.4	2.529	30.9
313	31.5	2.445	29.1
314	32.2	2.206	30.0
315	33.8	2.514	31.3
316	31.6	2.294	29.3
317	30.2	2.053	28.1
318	30.1	2.054	28.0
319	30.9	2.199	28.7
320	36.7	2.715	34.0
MEAN	**33.4**	**2.407**	**31.0**
S.D.	**2.47**	**0.25**	**2.26**

Individual Final Body and Liver Weights

Animal	FBW (g)	Liver (g)	FBW - Liver (g)
501	33.3	3.274	30.0
502	34.0	3.381	30.6
503	33.5	2.978	30.5
504	33.3	3.647	29.7
505	33.0	3.095	29.9
506	35.1	3.042	32.1
507	31.3	2.992	28.3
508	33.9	2.898	31.0
509	33.5	3.490	30.0
510	32.3	3.017	29.3
511	36.8	3.191	33.6
512	36.0	3.397	32.6
513	35.9	3.539	32.4
514	31.4	3.544	27.9
515	35.7	3.535	32.2
516	32.1	3.317	28.8
517	32.2	3.300	28.9
518	35.0	3.484	31.5
519	30.7	2.996	27.7
520	36.4	3.314	33.1
MEAN	**33.8**	**3.272**	**30.5**
S.D.	**1.81**	**0.23**	**1.76**
701	31.8	7.969	23.8
702	30.9	7.155	23.7
703	29.1	8.574	20.5
704	28.2	6.519	21.7
705	28.4	4.627	23.8
706	27.3	4.783	22.5
707	24.7	5.517	19.2
708	29.7	5.939	23.8
709	26.6	6.075	20.5
710	27.2	5.137	22.1
711	26.8	4.228	22.6
712	28.9	5.438	23.5
713	31.6	8.346	23.3
714	29.6	5.068	24.5
715	27.4	6.320	21.1
716	27.0	4.902	22.1
717	25.2	5.396	19.8
718	31.0	8.136	22.9
719	30.0	5.884	24.1
720	26.9	5.205	21.7
MEAN	**28.4**	**6.061**	**22.4**
S.D.	**2.04**	**1.32**	**1.53**

Individual Final Body and Liver Weights

Animal	FBW (g)	Liver (g)	FBW - Liver (g)
901	26.2	5.786	20.4
902	24.3	5.752	18.5
903	23.7	5.441	18.3
904	24.2	5.335	18.9
905	24.1	4.810	19.3
906	[a]	na	na
907	21.8	5.128	16.7
908	25.4	5.628	19.8
909	23.5	5.189	18.3
910	27.0	7.923	19.1
911	25.3	5.957	19.3
912	22.0	5.463	16.5
913	28.3	7.657	20.6
914	28.4	5.089	23.3
915	32.4	6.732	25.7
916	23.3	NW	na
917	29.4	6.316	23.1
918	28.0	5.574	22.4
919	27.1	5.895	21.2
920	29.5	6.499	23.0
MEAN	**26.0**	**5.899**	**20.2**
S.D.	**2.84**	**0.85**	**2.46**
1101	31.3	8.009	23.3
1102	39.5	8.361	31.1
1103	32.2	5.329	26.9
1104	30.4	6.914	23.5
1105	34.4	7.432	27.0
1106	27.2	6.657	20.5
1107	27.1	6.001	21.1
1108	32.3	7.295	25.0
1109	34.7	6.493	28.2
1110	24.9	5.491	19.4
1111	30.8	6.983	23.8
1112	[a]	na	na
1113	34.7	1.670	33.0
1114	30.4	6.359	24.0
1115	31.6	NW	na
1116	26.9	6.006	20.9
1117	27.5	6.827	20.7
1118	28.6	7.310	21.3
1119	26.2	4.637	21.6
1120	28.7	7.271	21.4
MEAN	**30.5**	**6.391**	**24.0**
S.D.	**3.66**	**1.51**	**3.84**

Appendix D
Individual Food Consumption

INDIVIDUAL FOOD CONSUMPTION

EXPLANATORY NOTES

ABBREVIATIONS:

Cons. - consumption
g/anm/day - grams of food consumed per animal per day

Individual Food Consumption

	Food Cons. g/anm/day Day 7	Food Cons. g/anm/day Day 14	Food Cons. g/anm/day Day 21	Food Cons. g/anm/day Day 28
Male, I 0 mg/kg				
101	4.9	4.7	4.7	4.5
102	5.6	5.6	5.9	5.8
103	5.2	5.4	5.2	4.5
104	4.5	4.7	4.9	4.2
105	5.3	4.9	5.4	4.5
106	4.5	5.4	5.3	5.1
107	4.3	5.0	5.1	4.9
108	4.7	4.6	4.7	4.1
109	5.1	5.0	4.8	3.9
110	5.5	5.5	5.2	4.6
111	4.9	5.0	4.8	4.3
112	5.3	4.7	5.0	4.4
113	5.6	4.9	4.8	4.3
114	5.1	4.5	4.7	4.8
115	4.5	4.9	4.9	4.8
116	4.8	5.2	5.2	5.0
118	5.0	5.3	5.6	5.3
119	5.4	5.7	5.6	5.1
120	5.9	5.3	5.4	5.1
Male, III 0.3 mg/kg				
301	5.3	5.5	5.5	5.4
302	5.3	5.6	5.3	4.9
303	5.1	6.0	5.3	5.2
304	5.6	5.7	5.6	5.4
305	5.1	5.4	5.6	5.3
306	4.5	4.9	5.1	4.6
307	4.6	4.8	4.9	4.9
308	4.7	4.6	4.7	4.5
309	5.2	5.2	5.0	4.3
310	5.9	5.6	5.3	5.4
311	5.7	5.4	5.5	5.2
312	5.2	5.4	5.2	5.1
313	5.5	5.8	5.3	4.9
314	4.9	5.2	5.1	4.7
315	5.1	5.2	4.8	4.9
316	4.7	4.5	3.9	4.3
317	4.9	5.0	4.8	4.4
318	4.6	5.0	4.6	5.1
319	5.1	4.9	4.9	4.8
320	5.5	5.0	5.2	5.4

Individual Food Consumption

	Food Cons. g/anm/day Day 7	Food Cons. g/anm/day Day 14	Food Cons. g/anm/day Day 21	Food Cons. g/anm/day Day 28
Male, V 1 mg/kg				
501	5.9	5.8	6.2	5.0
502	6.2	4.8	5.0	4.6
503	5.0	5.6	5.0	4.5
504	4.6	4.5	4.9	4.9
505	5.4	5.3	5.4	5.2
506	5.1	5.3	5.6	5.4
507	5.1	4.7	5.2	4.7
508	5.4	5.7	5.5	5.4
509	4.6	6.5	3.8	5.0
510	4.9	5.0	5.3	5.4
511	5.8	5.3	5.1	5.7
512	5.2	5.1	4.7	5.4
513	5.6	5.4	5.3	5.5
514	5.3	5.6	4.9	4.8
515	5.6	5.8	5.8	5.8
516	5.1	4.9	5.2	5.0
517	4.6	4.7	4.9	4.9
518	5.0	5.3	5.3	5.6
519	5.0	5.6	5.1	5.5
520	5.2	5.7	4.9	5.0
Male, VII 10 mg/kg				
701	5.2	6.7	6.9	6.4
702	5.9	6.2	6.4	5.0
703	5.0	5.9	5.1	4.5
704	5.8	6.0	6.1	6.1
705	5.1	6.6	5.7	5.1
706	5.0	5.4	5.2	5.2
707	4.4	3.4	4.4	4.3
708	4.7	6.9	6.1	6.1
709	5.7	6.9	6.5	5.7
710	5.3	5.7	5.4	4.5
711	3.9	5.3	4.4	5.8
712	4.4	6.5	5.9	5.4
713	5.4	6.3	4.5	4.1
714	3.8	5.9	5.5	6.7
715	5.0	5.4	5.0	6.2
716	4.8	5.2	5.5	5.5
717	4.7	5.0	4.7	4.7
718	5.5	6.2	4.0	5.9
719	5.0	6.5	4.1	5.9
720	5.6	4.9	4.2	6.9

Individual Food Consumption

	Food Cons. g/anm/day Day 7	Food Cons. g/anm/day Day 14	Food Cons. g/anm/day Day 21	Food Cons. g/anm/day Day 28
Male, IX 30 mg/kg				
901	3.7	5.7	4.5	4.8
902	3.7	5.4	2.5	3.7
903	4.7	4.5	4.0	4.4
904	3.3	5.7	NM	3.5
905	3.3	5.5	3.8	4.0
906	3.9			
907	3.2	3.7	3.5	3.2
908	4.7	6.1	4.2	5.6
909	4.8	5.9	3.8	4.1
910	5.0	5.2	4.5	4.7
911	5.1	5.8	4.4	5.7
912	5.3	4.7	3.1	3.7
913	4.8	4.9	4.1	3.9
914	5.1	5.7	4.7	5.1
915	5.7	6.7	7.2	7.3
916	3.9	6.1	4.2	4.6
917	5.9	7.0	7.1	7.3
918	4.9	6.0	5.1	4.9
919	4.3	5.6	4.5	4.6
920	5.3	6.4	3.9	5.2
Male, XI 30/0 mg/kg (Recovery)				
1101	5.2	6.4	6.1	6.1
1102	5.6	5.7	5.1	5.4
1103	5.6	5.4	3.9	5.7
1104	4.7	5.3	4.6	4.0
1105	5.1	7.7	6.2	6.0
1106	3.9	5.1	5.5	4.2
1107	4.4	4.4	3.6	4.3
1108	4.1	4.8	5.2	4.4
1109	4.3	7.8	4.9	7.5
1110	5.1	5.8	4.8	3.3
1111	4.1	4.4	3.9	4.5
1113	4.3	5.4	4.7	5.1
1114	5.0	5.9	5.5	6.7
1115	4.1	5.3	5.2	5.5
1116	3.0	4.2	3.8	5.0
1117	3.4	4.1	3.9	5.2
1118	4.4	5.8	4.1	6.8
1119	4.6	6.3	3.0	8.8
1120	3.9	5.1	3.4	5.9

Key: NM = Not Measurable

Appendix E
Individual Daily Animal Health Observations

Individual Daily Animal Health Observations

Sex	Group	Animal	Observation	Days
M	I	101	General observation, No Abnormality Detected	0-28
M	I	102	General observation, No Abnormality Detected	0-28
M	I	103	General observation, No Abnormality Detected	0-28
M	I	104	General observation, No Abnormality Detected	0-28
M	I	105	General observation, No Abnormality Detected	0-28
M	I	106	General observation, No Abnormality Detected	0-28
M	I	107	General observation, No Abnormality Detected	0-28
M	I	108	General observation, No Abnormality Detected	0-28
M	I	109	General observation, No Abnormality Detected	0-28
M	I	110	General observation, No Abnormality Detected	0-28
M	I	111	General observation, No Abnormality Detected	0-28
M	I	112	General observation, No Abnormality Detected	0-28
M	I	113	General observation, No Abnormality Detected	0-28
M	I	114	General observation, No Abnormality Detected	0-28
M	I	115	General observation, No Abnormality Detected	0-2,7-28
			Abnormal Gait, Hindlimb, Right, Severe	3-6
M	I	116	General observation, No Abnormality Detected	0-28
M	I	117	General observation, No Abnormality Detected	0-5
			Sacrificed *in extremis*	5
M	I	118	General observation, No Abnormality Detected	0-28
M	I	119	General observation, No Abnormality Detected	0-28
M	I	120	General observation, No Abnormality Detected	0-28
M	III	301	General observation, No Abnormality Detected	0-28
M	III	302	General observation, No Abnormality Detected	0-28
M	III	303	General observation, No Abnormality Detected	0-28
M	III	304	General observation, No Abnormality Detected	0-28
M	III	305	General observation, No Abnormality Detected	0-28
M	III	306	General observation, No Abnormality Detected	0-28
M	III	307	General observation, No Abnormality Detected	0-28
M	III	308	General observation, No Abnormality Detected	0-28
M	III	309	General observation, No Abnormality Detected	0-28
M	III	310	General observation, No Abnormality Detected	0-28
M	III	311	General observation, No Abnormality Detected	0-28
M	III	312	General observation, No Abnormality Detected	0-28
M	III	313	General observation, No Abnormality Detected	0-28
M	III	314	General observation, No Abnormality Detected	0-28
M	III	315	General observation, No Abnormality Detected	0-28
M	III	316	General observation, No Abnormality Detected	0-28
M	III	317	General observation, No Abnormality Detected	0-28
M	III	318	General observation, No Abnormality Detected	0-28
M	III	319	General observation, No Abnormality Detected	0-28
M	III	320	General observation, No Abnormality Detected	0-28

Individual Daily Animal Health Observations

Sex	Group	Animal	Observation	Days
M	V	501	General observation, No Abnormality Detected	0-28
M	V	502	General observation, No Abnormality Detected	0-28
M	V	503	General observation, No Abnormality Detected	0-28
M	V	504	General observation, No Abnormality Detected	0-28
M	V	505	General observation, No Abnormality Detected	0-28
M	V	506	General observation, No Abnormality Detected	0-28
M	V	507	General observation, No Abnormality Detected	0-28
M	V	508	General observation, No Abnormality Detected	0-28
M	V	509	General observation, No Abnormality Detected	0-28
M	V	510	General observation, No Abnormality Detected	0-28
M	V	511	General observation, No Abnormality Detected	0-28
M	V	512	General observation, No Abnormality Detected	0-28
M	V	513	General observation, No Abnormality Detected	0-28
M	V	514	General observation, No Abnormality Detected	0-28
M	V	515	General observation, No Abnormality Detected	0-28
M	V	516	General observation, No Abnormality Detected	0-28
M	V	517	General observation, No Abnormality Detected	0-28
M	V	518	General observation, No Abnormality Detected	0-28
M	V	519	General observation, No Abnormality Detected	0-28
M	V	520	General observation, No Abnormality Detected	0-28
M	VII	701	General observation, No Abnormality Detected	0-28
M	VII	702	General observation, No Abnormality Detected	0-28
M	VII	703	General observation, No Abnormality Detected	0-28
M	VII	704	General observation, No Abnormality Detected	0-28
M	VII	705	General observation, No Abnormality Detected	0-28
M	VII	706	General observation, No Abnormality Detected	0-28
M	VII	707	General observation, No Abnormality Detected	0-28
M	VII	708	General observation, No Abnormality Detected	0-28
M	VII	709	General observation, No Abnormality Detected	0-28
M	VII	710	General observation, No Abnormality Detected	0-28
M	VII	711	General observation, No Abnormality Detected	0-28
M	VII	712	General observation, No Abnormality Detected	0-28
M	VII	713	General observation, No Abnormality Detected	0-28
M	VII	714	General observation, No Abnormality Detected	0-4
			Swollen Observations, Shoulder, Left	5-28
M	VII	715	General observation, No Abnormality Detected	0-28
M	VII	716	General observation, No Abnormality Detected	0-28
M	VII	717	General observation, No Abnormality Detected	0-28
M	VII	718	General observation, No Abnormality Detected	0-28
M	VII	719	General observation, No Abnormality Detected	0-28
M	VII	720	General observation, No Abnormality Detected	0-28

Individual Daily Animal Health Observations

M	IX	901	General observation, No Abnormality Detected	0-8,12-28
			Comments, animal not dosed, pd obs not done	9-11
M	IX	902	General observation, No Abnormality Detected	0-8,12-22,28
			Comments, both ears, hindpaws/forepaws yellow	23-27
			Comments, animal not dosed, pd obs not done	9-11
M	IX	903	General observation, No Abnormality Detected	0-28
M	IX	904	General observation, No Abnormality Detected	0-28
M	IX	905	General observation, No Abnormality Detected	0-28
M	IX	906	General observation, No Abnormality Detected	0-6
			Swollen Observations, Shoulder, Left	7-8
			Sacrificed in extremis	9
M	IX	907	General observation, No Abnormality Detected	0-28
M	IX	908	General observation, No Abnormality Detected	0-21
			Comments, both ears/forepaws/hindpaws yellow	22-27
			Swollen Observations, Penis	22-28
M	IX	909	General observation, No Abnormality Detected	0-16,19-28
			Abnormal Gait, Hindlimb, Right, Moderate	17-18
M	IX	910	General observation, No Abnormality Detected	0-28
M	IX	911	General observation, No Abnormality Detected	0-27
			Comments, both ears/hindpaws/forepaws yellow	28
M	IX	912	General observation, No Abnormality Detected	0-28
M	IX	913	General observation, No Abnormality Detected	0-28
M	IX	914	General observation, No Abnormality Detected	0-28
M	IX	915	General observation, No Abnormality Detected	0-28
M	IX	916	General observation, No Abnormality Detected	0-28
M	IX	917	General observation, No Abnormality Detected	0-28
M	IX	918	General observation, No Abnormality Detected	0-28
M	IX	919	General observation, No Abnormality Detected	0-28
M	IX	920	General observation, No Abnormality Detected	0-28
M	XI	1101	General observation, No Abnormality Detected	0-28
M	XI	1102	General observation, No Abnormality Detected	0-28
M	XI	1103	General observation, No Abnormality Detected	0-28
M	XI	1104	General observation, No Abnormality Detected	0-28
M	XI	1105	General observation, No Abnormality Detected	0-28
M	XI	1106	General observation, No Abnormality Detected	0-28
M	XI	1107	General observation, No Abnormality Detected	0-28
M	XI	1108	General observation, No Abnormality Detected	0-8,12-21,28
			Comments, both ears/forepaws/hindpaws yellow	22-27
			Comments, animal not dosed, pd obs not done	9-11
			Stained Cageboard, Yellow	22-27
M	XI	1109	General observation, No Abnormality Detected	0-8, 12-17, 19-21,28
			Feces, Absent	18
			Comments, both ears/forepaws/hindpaws yellow	22-27
			Comments, animal not dosed, pd obs not done	9-11
			Stained Cageboard, Yellow	22-27
			Not Eating	18
M	XI	1110	General observation, No Abnormality Detected	0-28
M	XI	1111	General observation, No Abnormality Detected	0-28
M	XI	1112	General observation, No Abnormality Detected	0-2
			Eye Observations, Enophthalmus, Bilateral	3-5
			Lethargic	3-5
			Sacrificed in extremis	5
M	XI	1113	General observation, No Abnormality Detected	0-28
M	XI	1114	General observation, No Abnormality Detected	0-28
M	XI	1115	General observation, No Abnormality Detected	0-28
M	XI	1116	General observation, No Abnormality Detected	0-28
M	XI	1117	General observation, No Abnormality Detected	0-7,11-28
			Comments, animal not dosed, pd obs not done	8-10
M	XI	1118	General observation, No Abnormality Detected	0-28
M	XI	1119	General observation, No Abnormality Detected	0-28
M	XI	1120	General observation, No Abnormality Detected	0-7,11-28
			Comments, animal not dosed, pd obs not done	8-10

Appendix F
Individual Detailed Clinical Observations and Mortality Records

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	I	101	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	102	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	103	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	104	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	105	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	106	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	107	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	108	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	109	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	110	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	111	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	112	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	113	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	114	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	115	General observation, No Abnormality Detected	0,7-29
			Abnormal Gait, Hindlimb, Right, Severe	3
			Sacrificed by design	29
M	I	116	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	117	General observation, No Abnormality Detected	0
			Eye Observations, Enophthalmus, Bilateral	5
			Lethargic	5
			Breathing Observations, Labored	5
			Feces, Absent	5
			Comments, swollen thoracic ventral	5
			Swollen Observations, Face	5
			Swollen Observations, Neck	5
			Not Eating	5
			Sacrificed in extremis	5
M	I	118	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	119	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	I	120	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	III	301	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	302	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	303	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	304	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	305	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	306	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	307	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	308	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	309	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	310	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	311	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	312	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	313	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	314	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	315	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	316	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	317	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	318	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	319	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	III	320	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	V	501	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	502	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	503	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	504	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	505	General observation, No Abnormality Detected	0,14-29
			Abnormal Gait, Hindlimb, Left, Severe	7
			Sacrificed by design	29
M	V	506	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	507	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	508	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	509	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	510	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	511	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	512	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	513	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	514	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	515	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	516	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	517	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	518	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	519	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	V	520	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	VII	701	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	702	General observation, No Abnormality Detected	0,14-29
			Abnormal Gait, Hindlimb, Right, Moderate	7
			Sacrificed by design	29
M	VII	703	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	704	General observation, No Abnormality Detected	0-7,28-29
			Pale	14-21
			Sacrificed by design	29
M	VII	705	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	706	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	707	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	708	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	709	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	710	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	711	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	712	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	713	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	714	Absent, End of tail	0-29
			Swollen Observations, Shoulder, Left	7-29
			Sacrificed by design	29
M	VII	715	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	716	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	717	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	718	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	VII	719	General observation, No Abnormality Detected	0
			Misshapen Observations, Tail	7-29
			Sacrificed by design	29
M	VII	720	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	IX	901	General observation, No Abnormality Detected	0-14,28-29
			Pale	21
			Sacrificed by design	29
M	IX	902	General observation, No Abnormality Detected	0-14
			Pale	21-28
			Stain Fur/Skin, Perineum, Yellow	21-29
			Wet Fur, Perineum	21-28
			Sacrificed by design	29
M	IX	903	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	904	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	905	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	906	General observation, No Abnormality Detected	0-7
			Eye Observations, Partially Closed, Bilateral	9
			Lethargic	9
			Pale	9
			Sacrificed in extremis	9
M	IX	907	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	908	General observation, No Abnormality Detected	0-21
			Comments, both ears/hindpaws/forepaws yellow	28
			Swollen Observations, Penis	28-29
			Sacrificed by design	29
M	IX	909	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	910	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	911	General observation, No Abnormality Detected	0-21
			Comments, both ears/forepaws/hindpaws yellow	28-29
			Sacrificed by design	29
M	IX	912	General observation, No Abnormality Detected	0-14
			Pale	21-29
			Sacrificed by design	29
M	IX	913	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	914	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	915	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	916	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	917	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	918	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	919	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	IX	920	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Individual Detailed Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	XI	1101	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1102	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1103	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1104	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1105	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1106	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1107	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1108	General observation, No Abnormality Detected	0-21
			Comments, both ears yellow	28
			Stained Cageboard, Yellow	28-29
			Sacrificed by design	29
M	XI	1109	General observation, No Abnormality Detected	0-14
			Eye Observations, Enophthalmus, Bilateral	21
			Prostrate	21
			Comments, ears/extremities yellow	21
			Stained Cageboard, Yellow	28-29
			Sacrificed by design	29
M	XI	1110	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1111	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1112	General observation, No Abnormality Detected	0
			Eye Observations, Enophthalmus, Left	5
			Eye Observations, Dark, Bilateral	5
			Lethargic	5
			Feces, Absent	5
			Stain Fur/Skin, Perineum, Yellow	5
			Swollen Observations, Shoulder, Left	5
			Not Eating	5
			Sacrificed in extremis	5
M	XI	1113	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1114	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1115	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1116	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1117	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1118	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1119	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29
M	XI	1120	General observation, No Abnormality Detected	0-29
			Sacrificed by design	29

Appendix G
Individual Animal Clinical Pathology Data

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

General:

Adeq	-	adequate
CLOT or Clot	-	sample clotted
Decr	-	decreased
Mod	-	moderate
NSR	-	no sample received for testing
NP	-	not taken, not performed, or results not valid
OK	-	sample condition OK for testing
QNS	-	sample quantity not sufficient for testing
UTD	-	unable to determine

Individual Hematology Values:

COND	-	sample condition
RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular (cell) volume
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell

Individual Red Blood Cell Morphology Values:

ANIS	-	anisocytosis
MIC	-	microcytes
MAC	-	macrocytes
POLY	-	polychromasia
HYPO	-	hypochromasia
ECHI	-	echinocytes
ACAN	-	acanthocytes
TARG	-	target cells
RX	-	rouleaux
HJB	-	Howell-Jolly body
-	-	not observed

Individual White Blood Cell / Platelet Morphology Values:

SM	-	smudge white blood cells
TOX	-	toxic neutrophils
DB	-	Döhle bodies
VC	-	vacuolated cytoplasm
BC	-	basophilic cytoplasm
PCE	-	platelet clumps / estimate
GP	-	giant platelets
BP	-	bizarre platelets
-	-	not observed

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Individual Clinical Chemistry Values:

HEM	-	hemolysis
LIP	-	lipemia
ICT	-	icterus
CHOL	-	cholesterol
TRIG	-	triglycerides
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
HDL	-	high-density lipoprotein cholesterol
NHDL	-	non-high-density lipoprotein cholesterol
SCORT	-	serum corticosterone

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:
the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

Only positive findings were recorded for special observations (e.g., additional cell types) or observations marked other.

Individual Animal Clinical Pathology Data

Male, Group I 0 mg/kg Day 29

Animal	COND	RBC x10^6/µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10^3/µL	PLT x10^3/µL
101	OK	10.83	16.8	55.2	50.9	15.5	30.4	12.8	318.0	NP
102	OK	10.45	16.4	55.8	53.4	15.6	29.3	13.7	315.4	NP
103	OK	9.23	14.3	46.8	50.7	15.4	30.5	13.1	275.1	NP
104	OK	9.99	16.0	52.3	52.4	16.0	30.5	12.9	333.4	NP
105	OK	11.04	16.2	53.5	48.4	14.7	30.3	12.9	320.8	NP
106	OK	10.68	17.0	56.7	53.1	15.9	30.0	12.7	369.1	NP
107	OK	8.80	13.8	48.4	54.9	15.7	28.6	12.4	330.3	NP
108	OK	10.60	17.3	55.6	52.5	16.3	31.0	12.9	367.1	NP
109	OK	10.14	16.3	54.2	53.4	16.1	30.2	12.7	333.5	NP
110	OK	10.57	15.7	51.5	48.7	14.9	30.5	12.6	302.5	1177

Male, Group III 0.3 mg/kg Day 29

Animal	COND	RBC x10^6/µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10^3/µL	PLT x10^3/µL
301	OK	10.00	15.9	52.3	52.3	15.9	30.4	12.2	395.5	NP
302	OK	10.13	15.9	52.7	52.0	15.7	30.2	12.7	324.4	NP
303	OK	10.36	15.6	56.4	54.4	15.1	27.7	12.3	344.1	NP
304	OK	10.67	16.6	55.0	51.6	15.5	30.1	12.1	451.5	1545
305	OK	9.84	15.8	52.0	52.8	16.1	30.5	11.6	268.3	NP
306	OK	9.86	16.6	51.5	52.3	16.8	32.2	12.4	384.3	NP
307	OK	9.95	15.4	51.3	51.6	15.5	30.0	12.1	322.9	NP
308	OK	10.75	15.6	52.7	49.0	14.5	29.6	12.1	312.4	NP
309	OK	10.35	16.1	53.1	51.2	15.5	30.3	12.6	309.2	NP
310	OK	9.56	14.8	49.9	52.2	15.5	29.7	12.4	310.6	1259

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29				
Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
501	OK	9.55	15.9	52.9	55.4	16.6	30.0	11.2	220.0	NP
502	OK	10.51	15.6	54.8	52.2	14.8	28.5	12.4	364.0	NP
503	OK	9.83	15.3	49.0	49.9	15.5	31.2	12.4	288.9	1453
504	OK	10.08	15.5	50.9	50.5	15.4	30.4	11.7	342.3	NP
505	OK	9.63	14.6	48.5	50.3	15.1	30.1	12.5	211.4	NP
506	OK	9.28	15.3	50.6	54.5	16.4	30.2	13.1	300.3	NP
507	OK	5.37	8.2	27.8	51.7	15.4	29.7	11.2	159.6	705
508	OK	9.52	14.3	48.2	50.6	15.0	29.7	11.4	238.3	1125
509	OK	9.37	14.3	48.5	51.7	15.2	29.4	12.9	330.2	1481
510	OK	9.82	14.2	49.1	50.0	14.5	29.0	12.7	293.3	1114

Male,	Group	VII	10	mg/kg	Day	29				
Animal	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$
701	OK	10.49	16.3	57.6	54.9	15.5	28.2	11.9	338.1	NP
702	OK	9.83	14.9	51.7	52.6	15.2	28.8	11.4	302.9	NP
703	OK	9.92	16.7	55.2	55.7	16.8	30.1	11.9	248.3	NP
704	OK	8.09	11.9	41.7	51.5	14.7	28.4	12.2	162.0	NP
705	OK	10.47	14.7	52.8	50.5	14.0	27.8	12.7	171.9	NP
706	CLOT	NP	NP	NP	NP	NP	NP	NP	NP	NP
707	OK	11.34	16.3	54.7	48.2	14.3	29.7	11.6	278.5	NP
708	OK	10.69	15.7	53.4	50.0	14.7	29.4	12.7	271.3	NP
709	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP
710	OK	9.51	13.0	47.8	50.2	13.6	27.1	12.6	212.9	NP

Individual Animal Clinical Pathology Data

Male, Group IX 30 mg/kg Day 29

Animal	COND	RBC x10^6/µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10^3/µL	PLT x10^3/µL
901	OK	9.65	13.8	48.7	50.4	14.3	28.3	14.5	521.1	NP
902	OK	8.12	10.9	38.2	47.0	13.4	28.5	13.7	228.4	NP
903	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP
904	OK	9.57	14.0	47.7	49.9	14.6	29.3	12.3	181.0	NP
905	OK	9.61	13.4	46.0	47.8	13.9	29.1	12.7	245.7	NP
906	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP
907	OK	10.72	16.4	54.7	51.1	15.3	30.0	12.2	246.7	NP
908	OK	10.68	16.3	56.8	53.1	15.3	28.8	13.6	566.0	NP
909	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP
910	OK	9.15	13.8	46.0	50.3	15.1	30.0	12.9	463.7	NP

Male, Group XI 30/0 mg/kg (Recovery) Day 29

Animal	COND	RBC x10^6/µL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10^3/µL	PLT x10^3/µL
1101	OK	9.58	13.8	48.4	50.5	14.4	28.5	12.6	268.2	NP
1102	OK	8.13	12.6	43.3	53.3	15.5	29.0	13.6	374.0	NP
1103	OK	9.57	13.7	47.1	49.2	14.3	29.0	12.4	377.1	1530
1104	OK	8.37	13.3	45.2	54.0	15.9	29.5	12.7	703.1	1360
1105	OK	9.68	14.5	49.1	50.7	15.0	29.5	13.4	503.4	NP
1106	CLOT	NP	NP	NP	NP	NP	NP	NP	NP	NP
1107	OK	9.64	14.5	48.0	49.8	15.0	30.2	12.8	347.0	NP
1108	OK	8.34	12.4	43.2	51.8	14.9	28.8	13.3	625.5	NP
1109	OK	7.92	11.3	42.1	53.1	14.3	27.0	18.7	863.3	2434
1110	OK	8.15	11.5	38.4	47.1	14.1	30.1	16.7	275.3	679

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
101	6.96	0.84	5.84	0.21	0.07	0.00	0.00
102	4.12	0.48	3.47	0.04	0.07	0.02	0.04
103	5.04	0.50	4.54	0.00	0.00	0.00	0.00
104	10.08	1.75	7.79	0.16	0.26	0.04	0.09
105	6.20	0.69	5.26	0.06	0.11	0.01	0.06
106	12.10	1.32	10.17	0.20	0.25	0.05	0.11
107	7.98	0.71	6.94	0.09	0.11	0.02	0.10
108	6.21	0.43	5.53	0.19	0.06	0.00	0.00
109	9.05	0.72	7.79	0.27	0.27	0.00	0.00
110	7.75	0.54	6.98	0.08	0.16	0.00	0.00

Male,	Group	III	0.3	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
301	10.07	1.63	7.90	0.23	0.18	0.03	0.10
302	11.77	1.72	9.45	0.17	0.31	0.04	0.09
303	5.45	1.15	3.98	0.10	0.19	0.01	0.02
304	5.80	0.83	4.49	0.11	0.21	0.02	0.14
305	11.77	1.16	10.27	0.14	0.06	0.02	0.12
306	10.72	1.92	8.34	0.19	0.13	0.03	0.10
307	9.50	0.99	8.05	0.07	0.25	0.03	0.10
308	10.05	1.92	7.59	0.15	0.21	0.03	0.14
309	6.48	0.77	5.49	0.05	0.11	0.01	0.05
310	14.07	0.84	12.67	0.42	0.14	0.00	0.00

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
501	10.54	1.61	8.38	0.15	0.28	0.03	0.07
502	9.59	0.83	8.22	0.18	0.24	0.03	0.08
503	6.94	1.59	5.09	0.08	0.09	0.03	0.06
504	12.33	0.25	11.71	0.25	0.12	0.00	0.00
505	6.87	0.52	6.08	0.11	0.07	0.02	0.08
506	12.44	1.24	11.08	0.00	0.12	0.00	0.00
507	7.76	0.64	6.80	0.08	0.12	0.02	0.10
508	6.63	1.04	5.10	0.15	0.23	0.02	0.10
509	10.99	1.41	9.27	0.11	0.09	0.02	0.09
510	4.93	0.49	4.26	0.03	0.07	0.01	0.06

Male,	Group	VII	10	mg/kg	Day	29	
Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
701	12.71	2.29	9.69	0.34	0.08	0.06	0.25
702	8.33	2.67	5.00	0.58	0.08	0.00	0.00
703	11.31	1.81	8.71	0.68	0.11	0.00	0.00
704	9.79	1.20	8.12	0.19	0.05	0.03	0.20
705	15.71	2.57	12.52	0.23	0.13	0.05	0.21
706	NP	NP	NP	NP	NP	NP	NP
707	9.97	1.89	7.88	0.20	0.00	0.00	0.00
708	10.71	1.71	8.46	0.43	0.11	0.00	0.00
709	NP	NP	NP	NP	NP	NP	NP
710	10.55	1.00	8.94	0.30	0.10	0.03	0.17

Individual Animal Clinical Pathology Data

Male, Group IX 30 mg/kg Day 29

Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
901	11.69	3.99	6.83	0.50	0.09	0.07	0.21
902	6.02	2.82	2.83	0.18	0.05	0.01	0.12
903	NP	NP	NP	NP	NP	NP	NP
904	8.98	3.70	4.04	0.75	0.16	0.03	0.30
905	4.68	1.02	3.20	0.25	0.03	0.02	0.17
906	NP	NP	NP	NP	NP	NP	NP
907	5.31	1.70	3.18	0.32	0.11	0.00	0.00
908	5.05	1.67	3.13	0.25	0.00	0.00	0.00
909	NP	NP	NP	NP	NP	NP	NP
910	5.50	1.66	3.43	0.04	0.18	0.02	0.17

Male, Group XI 30/0 mg/kg (Recovery) Day 29

Animal	WBC $x10^3/\mu L$	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
1101	7.78	1.40	6.22	0.16	0.00	0.00	0.00
1102	7.28	1.72	5.03	0.28	0.08	0.01	0.15
1103	5.38	1.26	3.74	0.14	0.12	0.01	0.11
1104	7.55	2.34	4.71	0.09	0.09	0.05	0.27
1105	8.32	2.50	5.32	0.50	0.00	0.00	0.00
1106	NP	NP	NP	NP	NP	NP	NP
1107	8.24	2.60	4.85	0.13	0.27	0.11	0.29
1108	7.50	2.10	4.87	0.38	0.15	0.00	0.00
1109	5.67	1.66	3.71	0.09	0.06	0.03	0.13
1110	7.86	2.91	4.56	0.31	0.08	0.00	0.00

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
101	-	-	-	Few	-	-	-	-	-	-
102	-	-	-	Few	-	Trace	-	-	-	-
103	-	-	-	Few	-	-	-	-	-	-
104	-	-	-	Few	-	-	-	-	-	-
105	-	-	-	Few	-	-	-	-	-	-
106	-	-	-	Few	-	-	-	-	-	-
107	-	-	-	Few	-	-	-	-	-	-
108	-	-	-	Few	-	-	-	-	-	-
109	-	-	-	Few	-	-	-	-	-	-
110	-	-	-	Trace	-	-	-	-	-	-

Male,	Group	III	0.3	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
301	-	-	-	Few	-	-	-	-	-	-
302	-	-	-	Few	-	-	-	-	-	-
303	-	-	-	Few	-	-	-	-	-	-
304	-	-	-	Few	-	-	-	-	-	-
305	-	-	-	Trace	-	-	-	-	-	-
306	-	-	-	Few	-	-	-	-	-	-
307	-	-	-	Few	-	-	-	-	-	-
308	-	-	-	Trace	-	-	-	-	-	-
309	-	-	-	Few	-	-	-	-	-	-
310	-	-	-	Few	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
501	Trace	-	Trace	Trace	-	-	-	-	-	-
502	-	-	-	Few	-	-	-	-	-	-
503	-	-	-	Few	-	-	-	-	-	-
504	-	-	-	Few	-	-	-	-	-	-
505	-	-	-	-	-	-	-	-	-	-
506	-	-	-	Few	-	-	-	-	-	-
507	-	-	-	Trace	-	-	-	-	-	-
508	-	-	-	Trace	-	-	-	-	-	-
509	-	-	-	Few	-	-	-	-	-	-
510	-	-	-	Few	-	-	-	-	-	-

Male,	Group	VII	10	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
701	-	-	-	Few	-	-	-	-	-	-
702	-	-	-	Few	-	-	-	-	-	-
703	-	-	-	Trace	-	-	-	-	-	-
704	-	-	-	-	-	-	-	-	-	-
705	-	-	-	-	-	-	-	-	-	-
706	CLOT	NP	NP	NP	NP	NP	NP	NP	NP	NP
707	-	-	-	Trace	-	-	-	-	-	-
708	-	-	-	Trace	-	-	-	-	-	-
709	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP
710	-	-	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	IX	30	mg/kg	Day	29				
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
901	-	-	-	Mod	-	-	-	-	-	-
902	Trace	-	Trace	Trace	-	-	-	-	-	-
903	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP
904	-	-	-	-	-	-	-	-	-	-
905	-	-	-	Trace	-	-	-	-	-	-
906	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP
907	-	-	-	-	-	-	-	-	-	-
908	-	-	-	Mod	-	-	-	-	-	-
909	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP
910	-	-	-	Few	-	-	-	-	-	-

Male,	Group	XI	30/0	mg/kg	(Recovery)	Day	29			
Animal	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
1101	-	-	-	Mod	-	-	-	-	-	-
1102	Trace	Trace	Trace	Mod	-	-	-	-	-	-
1103	-	-	-	Few	-	-	-	-	-	-
1104	-	-	-	Mod	-	-	-	-	-	-
1105	-	-	-	Mod	-	-	-	-	-	-
1106	CLOT	NP	NP	NP	NP	NP	NP	NP	NP	NP
1107	Trace	Trace	Trace	Mod	-	-	-	-	-	-
1108	-	-	-	Many	-	-	-	-	-	-
1109	Trace	Trace	Trace	Many	-	-	-	-	-	-
1110	-	-	-	Few	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	I	0	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
101	-	-	-	-	-	Adeq	-	-
102	-	-	-	-	-	Adeq	-	-
103	-	-	-	-	-	Adeq	-	-
104	-	-	-	-	-	Adeq	-	-
105	-	-	-	-	-	Adeq	-	-
106	-	-	-	-	-	Adeq	-	-
107	-	-	-	-	-	Adeq	-	-
108	-	-	-	-	-	Decr	-	-
109	-	-	-	-	-	Adeq	-	-
110	-	-	-	-	-	-	-	-

Male,	Group	III	0.3	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
301	-	-	-	-	-	Adeq	-	-
302	-	-	-	-	-	Adeq	-	-
303	-	-	-	-	-	Adeq	-	-
304	-	-	-	-	-	-	-	-
305	-	-	-	-	-	Adeq	-	-
306	-	-	-	-	-	Adeq	-	-
307	-	-	-	-	-	Adeq	-	-
308	-	-	-	-	-	UTD	-	-
309	-	-	-	-	-	Adeq	-	-
310	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male,	Group	V	1	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
501	-	-	-	-	-	Adeq	-	-
502	-	-	-	-	-	Adeq	-	-
503	-	-	-	-	-	-	-	-
504	-	-	-	-	-	Decr	-	-
505	-	-	-	-	-	Adeq	-	-
506	-	-	-	-	-	Adeq	-	-
507	-	-	-	-	-	-	-	-
508	-	-	-	-	-	-	-	-
509	-	-	-	-	-	-	-	-
510	-	-	-	-	-	-	-	-

Male,	Group	VII	10	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
701	-	-	-	-	-	Adeq	-	-
702	-	-	-	-	-	Decr	-	-
703	-	-	-	-	-	Decr	-	-
704	-	-	-	-	-	Adeq	-	-
705	-	-	-	-	-	Adeq	-	-
706	CLOT	NP	NP	NP	NP	NP	NP	NP
707	-	-	-	-	-	Decr	-	-
708	-	-	-	-	-	Decr	-	-
709	QNS	NP	NP	NP	NP	NP	NP	NP
710	-	-	-	-	-	Decr	-	-

Individual Animal Clinical Pathology Data

Male,	Group	IX	30	mg/kg	Day	29		
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
901	-	-	-	-	-	Adeq	-	-
902	-	-	-	-	-	Adeq	-	-
903	QNS	NP	NP	NP	NP	NP	NP	NP
904	-	-	-	-	-	Adeq	-	-
905	-	-	-	-	-	Adeq	-	-
906	NSR	NP	NP	NP	NP	NP	NP	NP
907	-	-	-	-	-	Adeq	-	-
908	-	-	-	-	-	Decr	-	-
909	QNS	NP	NP	NP	NP	NP	NP	NP
910	-	-	-	-	-	Adeq	-	-

Male,	Group	XI	30/0	mg/kg	(Recovery)	Day	29	
Animal	SM	TOX	DB	VC	BC	PCE	GP	BP
1101	-	-	-	-	-	Adeq	-	-
1102	-	-	-	-	-	Adeq	-	-
1103	-	-	-	-	-	-	-	-
1104	-	-	-	-	-	-	-	-
1105	-	-	-	-	-	UTD	-	-
1106	CLOT	NP	NP	NP	NP	NP	NP	NP
1107	-	-	-	-	-	Adeq	-	-
1108	-	-	-	-	-	Adeq	-	-
1109	-	-	-	-	-	-	-	-
1110	-	-	-	-	-	-	-	-

Individual Animal Clinical Pathology Data

Male, Group I 0 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
101	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
102	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
103	None	None	None	NP	NP	5.8	3.0	2.8	NP	NP	204
104	Trace	None	None	NP	NP	5.6	3.0	2.6	NP	NP	NP
105	Small	None	None	NP	NP	5.5	3.0	2.5	NP	NP	NP
106	None	None	None	NP	NP	5.1	2.6	2.5	NP	NP	NP
107	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
108	None	None	None	NP	NP	5.9	3.0	2.9	NP	NP	NP
109	None	None	None	NP	NP	5.7	3.0	2.7	NP	NP	NP
110	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
111	None	None	None	161	178	NP	NP	NP	106	55	391
112	None	None	None	128	156	NP	NP	NP	83	45	282
113	None	None	None	110	170	NP	NP	NP	78	32	214
114	None	None	None	142	214	NP	NP	NP	91	51	99
115	None	None	None	98	133	NP	NP	NP	64	34	64
116	None	None	None	121	234	NP	NP	NP	80	41	120
117	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
118	None	None	None	131	162	NP	NP	NP	87	44	92
119	None	None	None	101	141	NP	NP	NP	68	33	110
120	None	None	None	62	118	NP	NP	NP	37	25	323

Individual Animal Clinical Pathology Data

Male, Group III 0.3 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
301	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
302	None	None	None	NP	NP	4.4	2.6	1.8	NP	NP	NP
303	None	None	None	NP	NP	5.5	3.0	2.5	NP	NP	NP
304	None	None	None	NP	NP	5.8	3.1	2.7	NP	NP	NP
305	None	None	None	NP	NP	5.4	2.8	2.6	NP	NP	NP
306	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
307	Small	None	None	NP	NP	5.6	3.0	2.6	NP	NP	NP
308	None	None	None	NP	NP	5.1	2.7	2.4	NP	NP	NP
309	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
310	None	None	None	NP	NP	4.7	2.4	2.3	NP	NP	NP
311	Small	None	None	132	190	NP	NP	NP	89	43	170
312	None	None	None	121	164	NP	NP	NP	72	49	212
313	None	None	None	101	112	NP	NP	NP	68	33	262
314	None	None	None	72	121	NP	NP	NP	52	20	236
315	None	None	None	140	187	NP	NP	NP	77	63	78
316	None	None	None	148	116	NP	NP	NP	87	61	231
317	None	None	None	122	141	NP	NP	NP	78	44	220
318	None	None	None	123	92	NP	NP	NP	80	43	360
319	None	None	None	104	136	NP	NP	NP	69	35	139
320	None	None	None	215	219	NP	NP	NP	96	119	76

Individual Animal Clinical Pathology Data

Male, Group V 1 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
501	None	None	None	NP	NP	5.4	3.2	2.2	NP	NP	NP
502	None	None	None	NP	NP	5.4	3.3	2.1	NP	NP	NP
503	None	None	None	NP	NP	6.6	3.3	3.3	NP	NP	NP
504	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
505	None	None	None	NP	NP	5.7	3.2	2.5	NP	NP	NP
506	None	None	None	NP	NP	5.4	3.1	2.3	NP	NP	NP
507	None	None	None	NP	NP	5.3	3.1	2.2	NP	NP	NP
508	None	None	None	NP	NP	5.3	2.9	2.4	NP	NP	NP
509	None	None	None	NP	NP	5.8	3.2	2.6	NP	NP	NP
510	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
511	Trace	None	None	138	151	NP	NP	NP	83	55	197
512	None	None	None	108	219	NP	NP	NP	59	49	127
513	None	None	None	86	103	NP	NP	NP	52	34	170
514	None	None	None	144	140	NP	NP	NP	68	76	32
515	None	None	None	57	118	NP	NP	NP	40	17	42
516	None	None	None	123	154	NP	NP	NP	63	60	247
517	None	None	None	91	207	NP	NP	NP	44	47	115
518	None	None	None	117	205	NP	NP	NP	57	60	48
519	None	None	None	88	152	NP	NP	NP	46	42	60
520	None	None	None	58	118	NP	NP	NP	34	24	43

Individual Animal Clinical Pathology Data

Male, Group VII 10 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
701	None	None	Trace	NP	NP	7.1	4.5	2.6	NP	NP	NP
702	None	None	Moderate	NP	NP	7.2	4.4	2.8	NP	NP	NP
703	Small	None	None	NP	NP	7.3	4.3	3.0	NP	NP	NP
704	None	None	Trace	NP	NP	7.0	4.2	2.8	NP	NP	NP
705	None	None	None	NP	NP	NP	NP	NP	NP	NP	NP
706	None	None	Trace	NP	NP	6.7	3.9	2.8	NP	NP	NP
707	None	None	Small	NP	NP	NP	NP	NP	NP	NP	NP
708	None	None	Trace	NP	NP	NP	NP	NP	NP	NP	NP
709	None	None	Small	NP	NP	7.0	4.2	2.8	NP	NP	NP
710	None	None	Trace	NP	NP	6.4	3.7	2.7	NP	NP	NP
711	None	None	Trace	63	60	NP	NP	NP	44	19	516
712	None	None	Trace	60	99	NP	NP	NP	38	22	471
713	None	None	Moderate	77	63	NP	NP	NP	50	27	605
714	None	None	None	113	65	NP	NP	NP	63	50	183
715	None	None	Trace	87	35	NP	NP	NP	55	32	259
716	None	None	None	66	131	NP	NP	NP	39	27	476
717	None	None	Small	96	103	NP	NP	NP	44	52	464
718	None	None	Trace	100	110	NP	NP	NP	53	47	578
719	None	None	Small	44	47	NP	NP	NP	28	16	216
720	None	None	Trace	106	64	NP	NP	NP	58	48	564

Individual Animal Clinical Pathology Data

Male, Group IX 30 mg/kg Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
901	None	None	Small	NP	NP	NP	NP	NP	NP	NP	NP
902	None	None	Moderate	NP	NP	6.1	4.0	2.1	NP	NP	NP
903	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
904	QNS	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
905	None	None	Moderate	NP	NP	NP	NP	NP	NP	NP	NP
906	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
907	None	None	Small	NP	NP	NP	NP	NP	NP	NP	NP
908	None	None	Moderate	NP	NP	5.4	3.4	2.0	NP	NP	NP
909	None	None	Moderate	NP	NP	NP	NP	NP	NP	NP	NP
910	None	None	Moderate	NP	NP	6.9	4.0	2.9	NP	NP	NP
911	None	None	Moderate	31	15	NP	NP	NP	26	5	912
912	None	None	Moderate	44	46	NP	NP	NP	22	22	597
913	None	None	Moderate	46	36	NP	NP	NP	23	23	503
914	None	None	Moderate	48	18	NP	NP	NP	33	15	141
915	None	None	Small	71	80	NP	NP	NP	38	33	264
916	None	None	Moderate	57	54	NP	NP	NP	27	30	821
917	None	None	Small	57	60	NP	NP	NP	37	20	434
918	None	None	Small	70	88	NP	NP	NP	38	32	414
919	None	None	Moderate	113	89	NP	NP	NP	59	54	130
920	None	None	Moderate	65	45	NP	NP	NP	40	25	158

Individual Animal Clinical Pathology Data

Male, Group XI 30/0 mg/kg (Recovery) Day 29

Animal	HEM	LIP	ICT	CHOL mg/dL	TRIG mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	HDL mg/dL	NHDL mg/dL	SCORT ng/mL
1101	None	None	Small	NP	NP	7.2	4.5	2.7	NP	NP	240
1102	None	None	None	NP	NP	7.3	4.2	3.1	NP	NP	25
1103	None	None	None	NP	NP	6.4	3.8	2.6	NP	NP	NP
1104	None	None	Trace	NP	NP	8.4	4.8	3.6	NP	NP	NP
1105	None	None	Small	NP	NP	7.9	4.6	3.3	NP	NP	NP
1106	Small	None	Trace	NP	NP	8.6	4.9	3.7	NP	NP	NP
1107	None	None	Small	NP	NP	NP	NP	NP	NP	NP	NP
1108	None	None	Small	NP	NP	7.8	4.3	3.5	NP	NP	NP
1109	None	None	Small	NP	NP	6.9	4.1	2.8	NP	NP	NP
1110	None	None	None	NP	NP	7.0	3.6	3.4	NP	NP	NP
1111	None	None	Trace	117	127	NP	NP	NP	64	53	78
1112	NSR	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
1113	None	None	Trace	93	111	NP	NP	NP	57	36	136
1114	None	None	Trace	121	110	NP	NP	NP	66	55	325
1115	None	None	Trace	121	115	NP	NP	NP	60	61	433
1116	Trace	None	Small	91	64	NP	NP	NP	55	36	NP
1117	None	None	Small	77	77	NP	NP	NP	47	30	194
1118	None	None	Trace	66	108	NP	NP	NP	38	28	183
1119	None	None	Trace	96	76	NP	NP	NP	57	39	476
1120	None	None	Trace	63	74	NP	NP	NP	36	27	501

Appendix H
Individual Primary Humoral Immune Response Data

INDIVIDUAL PRIMARY HUMORAL IMMUNE RESPONSE DATA

EXPLANATORY NOTES

FOOTNOTES:

b Serum was not collected from this animal, therefore, immune response could not be evaluated.
c Serum volume was insufficient for this animal, therefore, immune response could not be evaluated.
d This animal was not injected with the appropriate amount of SRBC, therefore, immune response could not be evaluated.

Individual Primary Humoral Immune Response Data

Animal Number	SLOPE	X	Log_2
Male, Group I - 0 mg/kg			
101	-1.0034	874	9.771
102	-0.9958	292	8.190
103	-0.9796	540	9.077
104	-0.8528	353	8.464
105	-0.9942	737	9.526
106	-0.8607	487	8.928
107	-0.8226	727	9.506
108	-0.9649	1018	9.992
109	-0.9366	417	8.704
110	-0.9625	777	9.602
111	-1.0109	340	8.409
112	-0.9652	784	9.615
113	-0.9896	537	9.069
114	-0.9866	497	8.957
115	-0.9834	384	8.585
116	-0.9607	689	9.428
117	[a]		
118	-0.9716	215	7.748
119	-0.8730	457	8.836
120	-0.8733	549	9.101
Male, Group III - 0.3 mg/kg			
301	-1.0351	681	9.412
302	-0.9020	235	7.877
303	-0.9403	405	8.662
304	-0.9653	445	8.798
305	-0.9268	258	8.011
306	[a]		
307	-1.0131	511	8.997
308	-0.9142	269	8.071
309	-0.9091	830	9.697
310	-0.9551	573	9.162
311	-0.9906	1205	10.235
312	-0.9573	645	9.333
313	-0.9484	417	8.704
314	-0.9460	793	9.631
315	-1.0128	401	8.647
316	-0.9552	552	9.109
317	-0.9239	132	7.044
318	-0.9189	579	9.177
319	-0.9709	211	7.721
320	-0.9938	622	9.281

Individual Primary Humoral Immune Response Data

Animal Number	SLOPE	X	Log_2
Male, Group V - 1 mg/kg			
501	-1.0294	324	8.340
502	-1.0045	562	9.134
503	-0.9279	428	8.741
504	-0.9200	353	8.464
505	-1.0255	343	8.422
506	-1.0013	161	7.331
507	-0.9730	284	8.150
508	-0.9931	444	8.794
509	-0.9765	223	7.801
510	-0.9230	331	8.371
511	-0.8852	673	9.394
512	-1.0076	222	7.794
513	-0.9627	317	8.308
514	-0.9910	363	8.504
515	-0.9622	734	9.520
516	-1.0029	351	8.455
517	-0.9352	205	7.679
518	-0.9065	151	7.238
519	-0.8622	253	7.983
520	-0.9383	220	7.781
Male, Group VII - 10 mg/kg			
701	-0.8465	285	8.155
702	-0.9652	95	6.570
703	[b]		
704	-0.9617	134	7.066
705	-1.0045	187	7.547
706	-0.9582	311	8.281
707	-1.0358	97	6.600
708	-1.0128	144	7.170
709	-1.0214	73	6.190
710	-0.9532	148	7.209
711	-0.7979	243	7.925
712	-0.9974	180	7.492
713	-1.0116	140	7.129
714	-0.9470	817	9.674
715	-0.8674	134	7.066
716	[c]		
717	-1.0155	226	7.820
718	-1.0207	110	6.781
719	-0.9787	7	2.807
720	-0.7775	230	7.845

Individual Primary Humoral Immune Response Data

Animal Number	SLOPE	X	Log_2
Male, Group IX - 30 mg/kg			
901	-0.9613	164	7.358
902	-0.9724	26	4.700
903	[a]		
904	[a]		
905	-1.0229	65	6.022
906	[a]		
907	[b]		
908	-1.0094	89	6.476
909	-0.9950	141	7.140
910	-1.0106	44	5.459
911	-0.9730	84	6.392
912	-1.0333	62	5.954
913	-0.8405	530	9.050
914	-0.9848	193	7.592
915	-0.9891	58	5.858
916	-1.0002	90	6.492
917	-0.9981	120	6.907
918	-1.0207	55	5.781
919	-0.9989	161	7.331
920	-0.9884	52	5.700
Male, Group IX - 30/0 mg/kg (Recovery)			
1101	-0.9921	89	6.476
1102	-1.0202	45	5.492
1103	-0.9938	114	6.833
1104	-1.0130	78	6.285
1105	-0.9951	96	6.585
1106	-0.9785	35	5.129
1107	-0.9904	88	6.459
1108	-0.9412	78	6.285
1109	-0.9771	47	5.555
1110	-0.8757	169	7.401
1111	-1.0060	43	5.426
1112	[a]		
1113	-0.9806	151	7.238
1114	-0.9696	74	6.209
1115	-0.9458	74	6.209
1116	[b]		
1117	-0.9999	167	7.384
1118	-0.9994	98	6.615
1119	-0.9866	52	5.700
1120	-0.9927	52	5.700

Appendix I
Individual Primary Humoral Immune Response Positive Control Data

Individual Primary Humoral Immune Response Positive Control Data

Animal Number	SLOPE	X	Log_2
Male, Group CI - Saline			
C101	-0.9624	578	9.175
C102	-0.9535	747	9.545
C103	-0.9312	417	8.704
C104	-0.9892	505	8.980
C105	-1.0066	268	8.066
C106	-0.8598	410	8.679
C107	-0.8395	140	7.129
C108	-0.9841	485	8.922
C109	-1.0023	429	8.745
C110	-0.9946	271	8.082
Male, Group CIII - 90 mg/kg Cyclophosphamide			
C301	-0.9579	25	4.644
C302	-0.9965	19	4.248
C303	-1.0234	25	4.644
C304	-0.8989	14	3.807
C305	-1.0583	14	3.807
C306	-0.9927	25	4.644
C307	-1.0321	33	5.044
C308	-0.9777	43	5.426
C309	-0.8206	8	3.000
C310	-1.0512	59	5.883
Male, Pooled Samples - Saline			
	-1.0107	405	8.662
Male, Pooled Samples - 90 mg/kg Cyclophosphamide			
	-0.9846	35	5.129

Appendix J
Individual Animal Final Body and Organ Weights

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS

EXPLANATORY NOTES

FOOTNOTES:

a An error occurred while weighing livers for this animal, and the liver weight was excluded from calculations.
b Liver inadvertently not weighed.

Individual Animal Final Body and Organ Weights

Group: IA Treatment: 0 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
101	31.00	0.409	1.3194	1.623	5.2355	396.82	0.106	0.3419	25.917	0.071	0.2290	17.359
102	34.70	0.460	1.3256	2.017	5.8127	438.48	0.110	0.3170	23.913	0.052	0.1499	11.304
103	33.40	0.480	1.4371	1.736	5.1976	361.67	0.124	0.3713	25.833	0.037	0.1108	7.7083
104	32.50	0.453	1.3938	1.768	5.4400	390.29	0.111	0.3415	24.503	0.058	0.1785	12.804
105	33.00	0.460	1.3939	1.459	4.4212	317.17	0.091	0.2758	19.783	0.047	0.1424	10.217
106	31.20	0.425	1.3622	1.717	5.5032	404.00	0.114	0.3654	26.824	0.051	0.1635	12.000
107	31.90	0.454	1.4232	1.861	5.8339	409.91	0.128	0.4013	28.194	0.041	0.1285	9.0308
108	30.30	0.462	1.5248	1.727	5.6997	373.81	0.107	0.3531	23.160	0.043	0.1419	9.3074
109	32.70	0.495	1.5138	1.711	5.2324	345.66	0.112	0.3425	22.626	0.057	0.1743	11.515
110	33.90	0.465	1.3717	1.634	4.8201	351.40	0.119	0.3510	25.591	0.050	0.1475	10.753
Mean	32.46	0.456	1.4065	1.725	5.3196	378.92	0.112	0.3461	24.634	0.051	0.1566	11.200
S.D.	1.38	0.025	0.0702	0.147	0.4455	35.880	0.010	0.0333	2.3978	0.010	0.0325	2.6437

Group: IB Treatment: 0 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
111	32.60	0.505	1.5491	1.801	5.5245	356.63	0.145	0.4448	28.713	0.052	0.1595	10.297
112	33.90	0.497	1.4661	a			0.122	0.3599	24.547	0.074	0.2183	14.889
113	34.60	0.461	1.3324	a			0.117	0.3382	25.380	0.043	0.1243	9.3275
114	33.70	0.498	1.4777	2.064	6.1246	414.46	0.115	0.3412	23.092	0.035	0.1039	7.0281
115	31.50	0.496	1.5746	1.718	5.4540	346.37	0.107	0.3397	21.573	0.061	0.1937	12.298
116	34.20	0.447	1.3070	1.795	5.2485	401.57	0.111	0.3246	24.832	0.044	0.1287	9.8434
118	34.50	0.503	1.4580	2.172	6.2957	431.81	0.099	0.2870	19.682	0.053	0.1536	10.537
119	34.30	0.492	1.4344	1.859	5.4198	377.85	0.152	0.4431	30.894	0.044	0.1283	8.9431
120	33.50	0.487	1.4537	1.639	4.8925	336.55	0.138	0.4119	28.337	0.045	0.1343	9.2402
Mean	33.64	0.487	1.4503	1.864	5.5657	380.75	0.123	0.3656	25.228	0.050	0.1494	10.267
S.D.	1.01	0.020	0.0873	0.190	0.4889	36.291	0.018	0.0552	3.5924	0.012	0.0365	2.2340

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
301	35.10	0.516	1.4701	2.609	7.4330	505.62	0.150	0.4274	29.070	0.052	0.1481	10.078
302	36.10	0.489	1.3546	2.405	6.6620	491.82	0.108	0.2992	22.086	0.043	0.1191	8.7935
303	37.40	0.486	1.2995	2.512	6.7166	516.87	0.104	0.2781	21.399	0.047	0.1257	9.6708
304	37.20	0.526	1.4140	2.758	7.4140	524.33	0.188	0.5054	35.741	0.048	0.1290	9.1255
305	34.50	0.516	1.4957	2.520	7.3043	488.37	0.117	0.3391	22.674	0.038	0.1101	7.3643
306	33.10	0.525	1.5861	2.539	7.6707	483.62	0.102	0.3082	19.429	0.034	0.1027	6.4762
307	31.30	0.473	1.5112	2.036	6.5048	430.44	0.095	0.3035	20.085	0.060	0.1917	12.685
308	33.70	0.436	1.2938	2.372	7.0386	544.04	0.129	0.3828	29.587	0.049	0.1454	11.239
309	29.90	0.441	1.4749	1.988	6.6488	450.79	0.112	0.3746	25.397	0.058	0.1940	13.152
310	32.80	0.455	1.3872	2.492	7.5976	547.69	0.130	0.3963	28.571	0.049	0.1494	10.769
Mean	34.11	0.486	1.4287	2.423	7.0990	498.36	0.124	0.3614	25.404	0.048	0.1415	9.9352
S.D.	2.45	0.034	0.0956	0.241	0.4378	37.749	0.028	0.0703	5.2317	0.008	0.0313	2.1325

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
311	36.60	0.452	1.2350	2.896	7.9126	640.71	0.114	0.3115	25.221	0.033	0.0902	7.3009
312	33.40	0.478	1.4311	2.529	7.5719	529.08	0.136	0.4072	28.452	0.040	0.1198	8.3682
313	31.50	0.477	1.5143	2.445	7.7619	512.58	0.076	0.2413	15.933	0.022	0.0698	4.6122
314	32.20	0.471	1.4627	2.206	6.8509	468.37	0.135	0.4193	28.662	0.045	0.1398	9.5541
315	33.80	0.505	1.4941	2.514	7.4379	497.82	0.152	0.4497	30.099	0.049	0.1450	9.7030
316	31.60	0.479	1.5158	2.294	7.2595	478.91	0.099	0.3133	20.668	0.054	0.1709	11.273
317	30.20	0.458	1.5166	2.053	6.7980	448.25	0.060	0.1987	13.100	0.057	0.1887	12.445
318	30.10	0.430	1.4286	2.054	6.8239	477.67	0.106	0.3522	24.651	0.031	0.1030	7.2093
319	30.90	0.459	1.4854	2.199	7.1165	479.08	0.060	0.1942	13.072	0.051	0.1650	11.111
320	36.70	0.493	1.3433	2.715	7.3978	550.71	0.151	0.4114	30.629	0.048	0.1308	9.7363
Mean	32.70	0.470	1.4427	2.391	7.2931	508.32	0.109	0.3299	23.049	0.043	0.1323	9.1314
S.D.	2.41	0.021	0.0908	0.280	0.3953	55.523	0.035	0.0940	6.9119	0.011	0.0375	2.3193

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: VA Treatment: 1 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
501	33.30	0.441	1.3243	3.274	9.8318	742.40	0.088	0.2643	19.955	0.037	0.1111	8.3900
502	34.00	0.522	1.5353	3.381	9.9441	647.70	0.135	0.3971	25.862	0.074	0.2176	14.176
503	33.50	0.479	1.4299	2.978	8.8896	621.71	0.090	0.2687	18.789	0.045	0.1343	9.3946
504	33.30	0.502	1.5075	3.647	10.952	726.49	0.108	0.3243	21.514	0.069	0.2072	13.745
505	33.00	0.444	1.3455	3.095	9.3788	697.07	0.092	0.2788	20.721	0.036	0.1091	8.1081
506	35.10	0.451	1.2849	3.042	8.6667	674.50	0.115	0.3276	25.499	0.062	0.1766	13.747
507	31.30	0.491	1.5687	2.992	9.5591	609.37	0.107	0.3419	21.792	0.056	0.1789	11.405
508	33.90	0.509	1.5015	2.898	8.5487	569.35	0.103	0.3038	20.236	0.054	0.1593	10.609
509	33.50	0.447	1.3343	3.490	10.418	780.76	0.112	0.3343	25.056	0.032	0.0955	7.1588
510	32.30	0.441	1.3653	3.017	9.3406	684.13	0.078	0.2415	17.687	0.040	0.1238	9.0703
Mean	33.32	0.473	1.4197	3.181	9.5529	675.35	0.103	0.3082	21.711	0.051	0.1514	10.580
S.D.	1.01	0.032	0.1017	0.252	0.7635	64.982	0.016	0.0462	2.8633	0.015	0.0429	2.5811

Group: VB Treatment: 1 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
511	36.80	0.497	1.3505	3.191	8.6712	642.05	0.081	0.2201	16.298	0.047	0.1277	9.4567
512	36.00	0.465	1.2917	3.397	9.4361	730.54	0.118	0.3278	25.376	0.049	0.1361	10.538
513	35.90	0.480	1.3370	3.539	9.8579	737.29	0.106	0.2953	22.083	0.045	0.1253	9.3750
514	31.40	0.508	1.6178	3.544	11.287	697.64	0.088	0.2803	17.323	0.037	0.1178	7.2835
515	35.70	0.459	1.2857	3.535	9.9020	770.15	0.124	0.3473	27.015	0.032	0.0896	6.9717
516	32.10	0.502	1.5639	3.317	10.333	660.76	0.088	0.2741	17.530	0.046	0.1433	9.1633
517	32.20	0.443	1.3758	3.300	10.248	744.92	0.093	0.2888	20.993	0.055	0.1708	12.415
518	35.00	0.484	1.3829	3.484	9.9543	719.83	0.114	0.3257	23.554	0.059	0.1686	12.190
519	30.70	0.424	1.3811	2.996	9.7590	706.60	0.109	0.3550	25.708	0.038	0.1238	8.9623
520	36.40	0.499	1.3709	3.314	9.1044	664.13	0.122	0.3352	24.449	0.059	0.1621	11.824
Mean	34.22	0.476	1.3957	3.362	9.8553	707.39	0.104	0.3050	22.033	0.047	0.1365	9.8179
S.D.	2.34	0.028	0.1092	0.177	0.7145	41.290	0.016	0.0412	3.8599	0.009	0.0254	1.9127

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: VIIA Treatment: 10 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
701	31.80	0.471	1.4811	7.969	25.060	1691.9	0.078	0.2453	16.561	0.029	0.0912	6.1571
702	30.90	0.477	1.5437	7.155	23.155	1500.0	0.081	0.2621	16.981	0.039	0.1262	8.1761
703	29.10	0.485	1.6667	8.574	29.464	1767.8	0.042	0.1443	8.6598	0.016	0.0550	3.2990
704	28.20	0.388	1.3759	6.519	23.117	1680.2	0.053	0.1879	13.660	0.035	0.1241	9.0206
705	28.40	0.439	1.5458	4.627	16.292	1054.0	0.058	0.2042	13.212	0.021	0.0739	4.7836
706	27.30	0.454	1.6630	4.783	17.520	1053.5	0.072	0.2637	15.859	0.035	0.1282	7.7093
707	24.70	0.414	1.6761	5.517	22.336	1332.6	0.054	0.2186	13.043	0.013	0.0526	3.1401
708	29.70	0.458	1.5421	5.939	19.997	1296.7	0.069	0.2323	15.066	0.030	0.1010	6.5502
709	26.60	0.465	1.7481	6.075	22.838	1306.5	0.045	0.1692	9.6774	0.010	0.0376	2.1505
710	27.20	0.389	1.4301	5.137	18.886	1320.6	0.076	0.2794	19.537	0.026	0.0956	6.6838
Mean	28.39	0.444	1.5673	6.230	21.867	1400.4	0.063	0.2207	14.226	0.025	0.0885	5.7670
S.D.	2.10	0.035	0.1193	1.331	3.8680	253.65	0.014	0.0442	3.3173	0.010	0.0328	2.3287

Group: VIIB Treatment: 10 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
711	26.80	0.427	1.5933	4.228	15.776	990.16	0.066	0.2463	15.457	0.014	0.0522	3.2787
712	28.90	0.478	1.6540	5.438	18.817	1137.7	0.082	0.2837	17.155	0.037	0.1280	7.7406
713	31.60	0.466	1.4747	8.346	26.411	1791.0	0.083	0.2627	17.811	0.017	0.0538	3.6481
714	29.60	0.455	1.5372	5.068	17.122	1113.8	0.128	0.4324	28.132	0.042	0.1419	9.2308
715	27.40	0.431	1.5730	6.320	23.066	1466.4	0.053	0.1934	12.297	0.020	0.0730	4.6404
716	27.00	0.436	1.6148	4.902	18.156	1124.3	0.052	0.1926	11.927	0.023	0.0852	5.2752
717	25.20	0.428	1.6984	5.396	21.413	1260.7	0.065	0.2579	15.187	0.026	0.1032	6.0748
718	31.00	0.436	1.4065	8.136	26.245	1866.1	0.064	0.2065	14.679	0.019	0.0613	4.3578
719	30.00	0.454	1.5133	5.884	19.613	1296.0	0.054	0.1800	11.894	0.027	0.0900	5.9471
720	26.90	0.477	1.7732	5.205	19.349	1091.2	0.046	0.1710	9.6436	0.019	0.0706	3.9832
Mean	28.44	0.449	1.5838	5.892	20.597	1313.7	0.069	0.2427	15.418	0.024	0.0859	5.4177
S.D.	2.09	0.020	0.1083	1.358	3.6430	301.90	0.024	0.0772	5.1497	0.009	0.0305	1.8903

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: IXA Treatment: 30 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
901	26.20	0.469	1.7901	5.786	22.084	1233.7	0.066	0.2519	14.072	0.009	0.0344	1.9190
902	24.30	0.414	1.7037	5.752	23.671	1389.4	0.034	0.1399	8.2126	0.022	0.0905	5.3140
903	23.70	0.448	1.8903	5.441	22.958	1214.5	0.021	0.0886	4.6875	0.017	0.0717	3.7946
904	24.20	0.420	1.7355	5.335	22.045	1270.2	0.031	0.1281	7.3810	0.028	0.1157	6.6667
905	24.10	0.415	1.7220	4.810	19.959	1159.0	0.037	0.1535	8.9157	0.023	0.0954	5.5422
907	21.80	0.401	1.8394	5.128	23.523	1278.8	0.026	0.1193	6.4838	0.015	0.0688	3.7406
908	25.40	0.435	1.7126	5.628	22.157	1293.8	0.037	0.1457	8.5057	0.065	0.2559	14.943
909	23.50	0.416	1.7702	5.189	22.081	1247.4	0.038	0.1617	9.1346	0.009	0.0383	2.1635
910	27.00	0.461	1.7074	7.923	29.344	1718.7	0.065	0.2407	14.100	0.027	0.1000	5.8568
Mean	24.47	0.431	1.7635	5.666	23.091	1311.7	0.039	0.1588	9.0548	0.024	0.0968	5.5489
S.D.	1.55	0.024	0.0656	0.903	2.5850	164.98	0.016	0.0541	3.1653	0.017	0.0656	3.8830

Group: IXB Treatment: 30 mg/kg Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
911	25.30	0.466	1.8419	5.957	23.545	1278.3	0.042	0.1660	9.0129	0.016	0.0632	3.4335
912	22.00	0.406	1.8455	5.463	24.832	1345.6	0.020	0.0909	4.9261	0.014	0.0636	3.4483
913	28.30	0.435	1.5371	7.657	27.057	1760.2	0.072	0.2544	16.552	0.025	0.0883	5.7471
914	28.40	0.431	1.5176	5.089	17.919	1180.7	0.082	0.2887	19.026	0.030	0.1056	6.9606
915	32.40	0.445	1.3735	6.732	20.778	1512.8	0.102	0.3148	22.921	0.039	0.1204	8.7640
916	23.30	0.419	1.7983	b			0.049	0.2103	11.695	0.023	0.0987	5.4893
917	29.40	0.462	1.5714	6.316	21.483	1367.1	0.068	0.2313	14.719	0.039	0.1327	8.4416
918	28.00	0.449	1.6036	5.574	19.907	1241.4	0.067	0.2393	14.922	0.029	0.1036	6.4588
919	27.10	0.459	1.6937	5.895	21.753	1284.3	0.067	0.2472	14.597	0.026	0.0959	5.6645
920	29.50	0.504	1.7085	6.499	22.031	1289.5	0.068	0.2305	13.492	0.014	0.0475	2.7778
Mean	27.37	0.448	1.6491	6.131	22.145	1362.2	0.064	0.2274	14.186	0.026	0.0920	5.7185
S.D.	3.09	0.028	0.1554	0.774	2.7075	175.82	0.022	0.0627	5.0057	0.009	0.0268	2.0510

FBW - Final Body Weight

Individual Animal Final Body and Organ Weights

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
1101	31.30	0.488	1.5591	8.009	25.588	1641.2	0.091	0.2907	18.648	0.027	0.0863	5.5328
1102	39.50	0.418	1.0582	8.361	21.167	2000.2	0.107	0.2709	25.598	0.048	0.1215	11.483
1103	32.20	0.426	1.3230	5.329	16.550	1250.9	0.069	0.2143	16.197	0.031	0.0963	7.2770
1104	30.40	0.424	1.3947	6.914	22.743	1630.7	0.086	0.2829	20.283	0.028	0.0921	6.6038
1105	34.40	0.432	1.2558	7.432	21.605	1720.4	0.081	0.2355	18.750	0.020	0.0581	4.6296
1106	27.20	0.468	1.7206	6.657	24.474	1422.4	0.058	0.2132	12.393	0.026	0.0956	5.5556
1107	27.10	0.386	1.4244	6.001	22.144	1554.7	0.060	0.2214	15.544	0.018	0.0664	4.6632
1108	32.30	0.436	1.3498	7.295	22.585	1673.2	0.067	0.2074	15.367	0.013	0.0402	2.9817
1109	34.70	0.448	1.2911	6.493	18.712	1449.3	0.104	0.2997	23.214	0.032	0.0922	7.1429
1110	24.90	0.446	1.7912	5.491	22.052	1231.2	0.091	0.3655	20.404	0.014	0.0562	3.1390
Mean	31.40	0.437	1.4168	6.798	21.762	1557.4	0.081	0.2602	18.640	0.026	0.0805	5.9009
S.D.	4.30	0.028	0.2203	1.010	2.5973	230.63	0.017	0.0510	3.9504	0.010	0.0244	2.4641

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

ANIMAL	FBW	BRAIN		LIVER			SPLEEN			THYMUS		
	(Gms)	(Gms)	%FBW	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN	(Gms)	%FBW	%BRAIN
1111	30.80	0.419	1.3604	6.983	22.672	1666.6	0.064	0.2078	15.274	0.032	0.1039	7.6372
1113	34.70	0.474	1.3660	1.670	4.8127	352.32	0.133	0.3833	28.059	0.037	0.1066	7.8059
1114	30.40	0.436	1.4342	6.359	20.918	1458.5	0.048	0.1579	11.009	0.045	0.1480	10.321
1115	31.60	0.466	1.4747	b			0.086	0.2722	18.455	0.025	0.0791	5.3648
1116	26.90	0.418	1.5539	6.006	22.327	1436.8	0.062	0.2305	14.833	0.034	0.1264	8.1340
1117	27.50	0.490	1.7818	6.827	24.825	1393.3	0.072	0.2618	14.694	0.023	0.0836	4.6939
1118	28.60	0.425	1.4860	7.310	25.559	1720.0	0.065	0.2273	15.294	0.026	0.0909	6.1176
1119	26.20	0.413	1.5763	4.637	17.698	1122.8	0.052	0.1985	12.591	0.016	0.0611	3.8741
1120	28.70	0.480	1.6725	7.271	25.334	1514.8	0.055	0.1916	11.458	0.020	0.0697	4.1667
Mean	29.49	0.447	1.5229	5.883	20.518	1333.1	0.071	0.2368	15.741	0.029	0.0966	6.4573
S.D.	2.67	0.030	0.1396	1.913	6.8645	435.92	0.026	0.0652	5.1490	0.009	0.0278	2.1590

FBW - Final Body Weight

Appendix K
Individual Animal Pathology Data

INDIVIDUAL ANIMAL PATHOLOGY DATA

KEY TO APPENDIX

LESION GRADING:

Histopathology changes are described according to their morphologic character, distribution and severity. The distribution (extent of tissue involvement) is indicated, where appropriate, by modifiers such as focal, multifocal, diffuse, unilateral, bilateral, etc. A severity score, if appropriate, is also assigned as follows:

MINIMAL: The amount of change present barely exceeds that which is considered to be within normal limits.

MILD: In general, the lesion is easily identified but of limited severity. The lesion probably does not produce any functional impairment.

MODERATE: The lesion is prominent but there is significant potential for increased severity. Limited tissue or organ dysfunction is possible.

SEVERE: The degree of change is either as complete as considered possible or great enough in intensity or extent to expect significant tissue or organ dysfunction.

COMMENT:

Grades minimal through severe represent progressive involvement/severity along a continuum with minimal lesions being the least severe and severe lesions being the most severe. While the grades refer to the morphologic characteristics of lesions, they also indicate their relative biologic significance.

Gross observations listing multiple masses for a tissue are distinguished with letters (i.e., a, b, c, d, etc.).

Individual Animal Pathology Data

Group: IA Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
101	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
FATTY CHANGE, DIFFUSE, mild.
THYMUS :
ECTOPIC THYROID.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

102	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

102 Continued on the next page ....

Individual Animal Pathology Data

Group: IA Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
102	Continued from previous page
	Histopathology :
	LYMPH NODE - POPLITEAL :
	NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed :
	LIVER, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
103	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	SPLEEN :
	HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	LYMPH NODE - POPLITEAL :
	NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed :
	LIVER, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
104	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

104 Continued on the next page ....

Individual Animal Pathology Data

Group: IA Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
104	Continued from previous page
	Histopathology :
	CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
105	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
106	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

106 Continued on the next page ....

Individual Animal Pathology Data

Group: IA Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
106	Continued from previous page

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, BONE MARROW

107 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, BONE MARROW

108 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

108 Continued on the next page ....

Individual Animal Pathology Data

Group: IA Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
108	Continued from previous page
	Histopathology :
	CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
109	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : FATTY CHANGE, DIFFUSE, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
110	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

110 Continued on the next page ....

Individual Animal Pathology Data

Group: IA Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
110	Continued from previous page

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

Individual Animal Pathology Data

Group: IB Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
111	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	SPLEEN : HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : LIVER, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
112	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Group: IB Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
113	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Animal Ref	Microscopic & Macroscopic Findings
114	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

114 Continued on the next page ....

Individual Animal Pathology Data

Group: IB Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
114	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : LIVER, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
115	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	SPLEEN : HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : LIVER, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
116	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

116 Continued on the next page ....

Individual Animal Pathology Data

Group: IB Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
116	Continued from previous page

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

117 Unscheduled Sacrifice
Duration of dosing-days: 5
Exposure Group : Early Deaths
Animal is signed off from necropsy

Gross Pathology :

TRACHEA :
RUPTURE.
ESOPHAGUS :
RUPTURE.
SKIN :
OTHER, abscess subcutaneous axilla right,subcutaneous air pocket, dorsal neck, right axilla.

No Macroscopic Abnormality Observed :
LIVER

Histopathology :

MESENTERIC LYMPH NODE :
DEPLETION/ATROPHY, LYMPHOID, minimal, (outer cortex and follicles).
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, mild.
ESOPHAGUS :
INFLAMMATION, MYOFIBER, mild, (due to esophageal rupture).
SKIN :
Moderate, ABSCESS.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, moderate.

117 Continued on the next page ....

Individual Animal Pathology Data

Group: IB Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
117	Continued from previous page
	Histopathology :
	CAUSE OF DEATH :
	DOSING ACCIDENT.
	MEDIASTINUM :
	INFLAMMATION, CHRONIC, (due to esophageal rupture).
	LYMPH NODE - POPLITEAL :
	NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, TRACHEA, FEMUR/KNEE JOINT, STERNUM
118	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, BONE MARROW
119	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

119 Continued on the next page ....

Individual Animal Pathology Data

Group: IB Treatment: 0 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
119	Continued from previous page
	Histopathology :
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, BONE MARROW
120	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	SPLEEN :
	HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	LIVER, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE
	JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
301	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
302	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.

302 Continued on the next page ....

Individual Animal Pathology Data

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
302	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
303	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
304	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
304	Continued from previous page
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
305	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
306	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

306 Continued on the next page ....

Individual Animal Pathology Data

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
306	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

307 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
308	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. INFLAMMATION, SUBACUTE/CHRONIC, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
309	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.

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Individual Animal Pathology Data

Group: IIIA Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
309	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
310	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with
	cytoplasmic eosinophilic stippling.
	NECROSIS, FOCAL, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
311	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. SPLEEN : HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
312	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.

312 Continued on the next page ....

Individual Animal Pathology Data

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
312	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
313	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
314	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
314	Continued from previous page
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
315	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
	SPLEEN :
	HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
316	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

317	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

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Individual Animal Pathology Data

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
317	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
318	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
319	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Group: IIIB Treatment: 0.3 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
319	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

320 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, mild, with cytoplasmic eosinophilic stippling.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VA Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
501	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
502	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, minimal. SPLEEN : HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.

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Individual Animal Pathology Data

Group: VA Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
502	Continued from previous page
	Histopathology :
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
503	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with
	cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
504	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Group: VA Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
504	Continued from previous page
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	THYMUS :
	HYPERPLASIA, LYMPHOID, FOLLICULAR, mild.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW
505	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VA Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
506	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
507	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.

507 Continued on the next page ....

Individual Animal Pathology Data

Group: VA Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
507	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
508	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, FOCAL, minimal. INFLAMMATION, SUBACUTE/CHRONIC, minimal. NECROSIS, INDIVIDUAL CELL, INCREASED, mild. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
509	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Group: VA Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
509	Continued from previous page
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
510	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VB Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
511	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
512	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling. NECROSIS, FOCAL, minimal. NECROSIS, INDIVIDUAL CELL, INCREASED, minimal. MESENTERIC LYMPH NODE : NOT PRESENT.

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Individual Animal Pathology Data

Group: VB Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
512	Continued from previous page
	Histopathology :
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, THYMUS, BONE MARROW
513	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with
	cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
514	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

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Individual Animal Pathology Data

Group: VB Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
514	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
NECROSIS, FOCAL, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

515 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VB Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
516	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with
cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
THYMUS :
NOT PRESENT.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW

517	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with
cytoplasmic eosinophilic stippling.

517 Continued on the next page ....

Individual Animal Pathology Data

Group: VB Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
517	Continued from previous page
	Histopathology :
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
518	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with
	cytoplasmic eosinophilic stippling.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
519	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS,
	FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

519 Continued on the next page ....

Individual Animal Pathology Data

Group: VB Treatment: 1 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
519	Continued from previous page
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
520	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
701	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERPLASIA, BILE DUCT, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, mild. Minimal, FATTY CHANGE, NONZONAL. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
702	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

702 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
702	Continued from previous page
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
	Minimal, FATTY CHANGE, NONZONAL.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
703	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	LARGE.
	SPLEEN :
	SMALL.
	No Macroscopic Abnormality Observed :
	BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	NECROSIS, FOCAL, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	HYPERPLASIA, BILE DUCT, minimal.

703 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
703	Continued from previous page

Histopathology :

THYMUS :
DEPLETION/ATROPHY, LYMPHOID, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW

704 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT,
STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with
cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
Minimal, FATTY CHANGE, NONZONAL.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
705	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Animal Ref	Microscopic & Macroscopic Findings
706	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

706 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
706	Continued from previous page
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
	Minimal, FATTY CHANGE, NONZONAL.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
707	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	LARGE.
	SPLEEN :
	SMALL.
	THYMUS :
	SMALL.
	No Macroscopic Abnormality Observed :
	BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.

707 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
707	Continued from previous page
	Histopathology :
	THYMUS :
	ECTOPIC THYROID.
	DEPLETION/ATROPHY, LYMPHOID, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW
708	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	LARGE.
	No Macroscopic Abnormality Observed :
	SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
	Minimal, FATTY CHANGE, NONZONAL.
	THYMUS :
	DEPLETION/ATROPHY, LYMPHOID, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
709	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.
THYMUS :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
Minimal, FATTY CHANGE, NONZONAL.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW

710	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

710 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIA Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
710	Continued from previous page

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
711	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : NECROSIS, INDIVIDUAL CELL, INCREASED, mild. MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. Minimal, FATTY CHANGE, NONZONAL. THYMUS : NOT PRESENT. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW
712	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

712 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
712	Continued from previous page

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

713 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
DISCOLORATION, TAN, 1CM DIA.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, FOCAL, moderate.
HYPERPLASIA, BILE DUCT, minimal.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.

713 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
713	Continued from previous page
	Histopathology :
	THYMUS :
	DEPLETION/ATROPHY, LYMPHOID, minimal.
	BONE MARROW :
	HYPERPLASIA, GRANULOCYTIC, minimal.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	MESENTERIC LYMPH NODE
714	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	LARGE.
	SKIN :
	MASS, GREEN, AXILLA, LEFT, 1.5CM DIA.
	No Macroscopic Abnormality Observed :
	SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	SPLEEN :
	HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
	SKIN :
	Moderate, ABSCESS.
	BONE MARROW :
	HYPERPLASIA, GRANULOCYTIC, moderate.

714 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
714	Continued from previous page

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
MESENTERIC LYMPH NODE, THYMUS

715 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, BONE MARROW

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
716	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : NECROSIS, INDIVIDUAL CELL, INCREASED, minimal. HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. NECROSIS, FOCAL, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW
717	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE. SPLEEN : SMALL. THYMUS : SMALL.
	No Macroscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

717 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
717	Continued from previous page

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
MESENTERIC LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, THYMUS, BONE MARROW

718 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

718 Continued on the next page ....

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
718	Continued from previous page

Histopathology :

LIVER :
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
MESENTERIC LYMPH NODE, BONE MARROW

719 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE, THYMUS, BONE MARROW

Individual Animal Pathology Data

Group: VIIB Treatment: 10 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
720	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, FOCAL, mild.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, minimal.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, MESENTERIC LYMPH NODE

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
901	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

902	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

902 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
902	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
Minimal, FATTY CHANGE, NONZONAL.
THYMUS :
NOT PRESENT.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM

903 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.
THYMUS :
SMALL.

903 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
903	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
Minimal, FATTY CHANGE, NONZONAL.
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

904	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

904 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
904	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
MESENTERIC LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, FEMUR/KNEE JOINT, STERNUM, LYMPH NODE - POPLITEAL

905 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

905 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
905	Continued from previous page

Gross Pathology :

SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
MESENTERIC LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, severe.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

906 Unscheduled Sacrifice
Duration of dosing-days: 9
Exposure Group : Early Deaths
Animal is signed off from necropsy

Gross Pathology :

LIVER :
DISCOLORATION, PALE, MOTTLED, DIFFUSE.

906 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
906	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, moderate, with cytoplasmic eosinophilic stippling.
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
FATTY CHANGE, PERIPORTAL, minimal.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, moderate, (periarteriolar lymphoid sheath).
MESENTERIC LYMPH NODE :
DEPLETION/ATROPHY, LYMPHOID, moderate, (inner cortex and outer cortex).
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, severe.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, moderate, with left shift (immature).
CAUSE OF DEATH :
UNDETERMINED.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, FEMUR/KNEE JOINT, STERNUM

907 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

907 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
907	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
MESENTERIC LYMPH NODE :
DEPLETION/ATROPHY, LYMPHOID, mild, (inner cortex, outer cortex, and follicles).
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT.

No Microscopic Abnormality Observed :
BRAIN, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

908 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

908 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
908	Continued from previous page

Gross Pathology :

LIVER :
DISCOLORATION, TAN, MOTTLED.
SPLEEN :
SMALL.
PENIS :
PARAPHIMOSIS.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, FOCAL, moderate, coagulative, subcapsular.
HYPERPLASIA, BILE DUCT, mild.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
PENIS :
EROSION/ULCER, moderate.
PREPUTIAL GLANDS :
ECTASIA, mild.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

908 Continued on the next page ....

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
908	Continued from previous page

Histopathology :

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM

909 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.
THYMUS :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM,
POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with
cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, severe.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT,
STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

Individual Animal Pathology Data

Group: IXA Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
910	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
DISCOLORATION, TAN, MOTTLED, LEFT.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
DEPLETION/ATROPHY, LYMPHOID, mild, (periarteriolar lymphoid sheath).
THYMUS :
NOT PRESENT.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
911	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, severe.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
912	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, mild. MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal. HYPERPLASIA, BILE DUCT, minimal. Minimal, FATTY CHANGE, NONZONAL. THYMUS : NOT PRESENT IN MEDIASTINAL TISSUE. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
913	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE. DISCOLORATION, TAN, RIGHT, ACCESSORY.

913 Continued on the next page ....

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
913	Continued from previous page

Gross Pathology :

MESENTERIC LYMPH NODE :
SMALL.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
NECROSIS, FOCAL, moderate, coagulative, subcapsular.
HYPERPLASIA, BILE DUCT, mild.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, moderate.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

914 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

914 Continued on the next page ....

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
914	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with
cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE
JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

915 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
DISCOLORATION, LEFT, 1MM DIA.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE
JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with
cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.

915 Continued on the next page ....

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
915	Continued from previous page
	Histopathology :
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed :
	BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT,
	STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
916	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	DISCOLORATION, TAN, CAUDATE, 0.3 CM DIA.
	LARGE.
	No Macroscopic Abnormality Observed :
	SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE
	JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with
	cytoplasmic eosinophilic stippling.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
	NECROSIS, FOCAL, moderate, coagulative, subcapsular.
	INFLAMMATION, SUBACUTE/CHRONIC, minimal.
	HYPERPLASIA, BILE DUCT, minimal.
	Minimal, FATTY CHANGE, NONZONAL.
	THYMUS :
	DEPLETION/ATROPHY, LYMPHOID, mild.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.

916 Continued on the next page ....

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
916	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
917	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, mild. NECROSIS, FOCAL, minimal, coagulative, subcapsular. HYPERPLASIA, BILE DUCT, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
918	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. HYPERPLASIA, BILE DUCT, minimal. NECROSIS, INDIVIDUAL CELL, INCREASED, mild. MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal. SPLEEN : DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath). CAUSE OF DEATH : SACRIFICE BY DESIGN.
	No Microscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL
919	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.

919 Continued on the next page ....

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
919	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, LYMPH NODE - POPLITEAL

920 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.

920 Continued on the next page ....

Individual Animal Pathology Data

Group: IXB Treatment: 30 mg/kg Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
920	Continued from previous page

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1101	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild.
HYPERPLASIA, BILE DUCT, minimal.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1102	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
HYPERPLASIA, BILE DUCT, minimal.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
MESENTERIC LYMPH NODE :
NOT PRESENT IN TISSUE SECTION.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, THYMUS, FEMUR/KNEE JOINT, STERNUM

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1103	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM

1104	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

1104 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1104	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
THYMUS :
CYST, EPITHELIAL, minimal.
BONE MARROW :
HYPERPLASIA, ERYTHROCYTIC, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, LYMPH NODE - POPLITEAL

1105 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

1105 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1105	Continued from previous page
	Gross Pathology :
	No Macroscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER :
	HYPERPLASIA, BILE DUCT, minimal.
	MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
	NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
	HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
	SPLEEN :
	HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
	BONE MARROW :
	HYPERPLASIA, ERYTHROCYTIC, mild.
	CAUSE OF DEATH :
	SACRIFICE BY DESIGN.
	LYMPH NODE - POPLITEAL :
	NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM
1106	Terminal Sacrifice
	Killed on Day : 29
	Exposure Group : SD
	Animal is signed off from necropsy
	Gross Pathology :
	LIVER :
	LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

1106 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1106	Continued from previous page

Histopathology :

LIVER :
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
HYPERPLASIA, BILE DUCT, minimal.
THYMUS :
CYST, EPITHELIAL, minimal.
DEPLETION/ATROPHY, LYMPHOID, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

1107 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
THYMUS :
SMALL.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.

1107 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1107	Continued from previous page

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM,
BONE MARROW

1108 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
THYMUS :
SMALL.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT,
STERNUM, POPLITEAL LYMPH NODE

1108 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1108	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

1109 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.

1109 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1109	Continued from previous page

Histopathology :

LIVER :
HYPERPLASIA, BILE DUCT, minimal.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, moderate.
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
BONE MARROW :
HYPERPLASIA, ERYTHROCYTIC, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM

1110 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
DISCOLORATION, TAN, LEFT, NECROTIC 6MM DIAM.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

1110 Continued on the next page ....

Individual Animal Pathology Data

Group: XIA Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1110	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, FOCAL, moderate, coagulative, subcapsular.
HYPERPLASIA, BILE DUCT, minimal.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, mild, (periarteriolar lymphoid sheath).
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, moderate.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, moderate.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1111	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
Minimal, FATTY CHANGE, NONZONAL.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

1112	Unscheduled Sacrifice Duration of dosing-days: 5 Exposure Group : Early Deaths Animal is signed off from necropsy

Gross Pathology :

ESOPHAGUS :
RUPTURE.
SKIN :
OTHER, ABSCESS AXILLA RIGHT.

1112 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1112	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, minimal, with cytoplasmic eosinophilic stippling.
FATTY CHANGE, DIFFUSE, minimal.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, moderate, (periarteriolar lymphoid sheath).
MESENTERIC LYMPH NODE :
DEPLETION/ATROPHY, LYMPHOID, mild.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, severe.
BONE MARROW :
HYPERPLASIA, GRANULOCYTIC, moderate, with left shift (immature).
CAUSE OF DEATH :
DOSING ACCIDENT.

No Microscopic Abnormality Observed :
BRAIN, FEMUR/KNEE JOINT, STERNUM, LYMPH NODE - POPLITEAL

1113 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

1113 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1113	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

1114 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.
SPLEEN :
SMALL.

No Macroscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
HYPERPLASIA, BILE DUCT, minimal.

1114 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1114	Continued from previous page

Histopathology :

LIVER :
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

1115 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
SPLEEN :
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.

1115 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1115	Continued from previous page

Histopathology :

CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

1116 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
NECROSIS, INDIVIDUAL CELL, INCREASED, mild.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
NECROSIS, FOCAL, minimal, coagulative, subcapsular.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, mild.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, severe.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.
LYMPH NODE - POPLITEAL :
NOT PRESENT IN TISSUE SECTION.

1116 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1116	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
1117	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, mild. MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild. HYPERPLASIA, BILE DUCT, minimal. INFLAMMATION, SUBACUTE/CHRONIC, minimal. Minimal, FATTY CHANGE, NONZONAL. SPLEEN : HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN. LYMPH NODE - POPLITEAL : NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed : BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1118	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.
	No Macroscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE
	Histopathology :
	LIVER : HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling. NECROSIS, INDIVIDUAL CELL, INCREASED, minimal. MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal. HYPERPLASIA, BILE DUCT, minimal. CAUSE OF DEATH : SACRIFICE BY DESIGN. LYMPH NODE - POPLITEAL : NOT PRESENT IN TISSUE SECTION.
	No Microscopic Abnormality Observed : SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, BONE MARROW
1119	Terminal Sacrifice Killed on Day : 29 Exposure Group : SD Animal is signed off from necropsy
	Gross Pathology :
	LIVER : LARGE.

1119 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1119	Continued from previous page

Gross Pathology :

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, mild.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
DEPLETION/ATROPHY, LYMPHOID, minimal, (periarteriolar lymphoid sheath).
THYMUS :
NOT PRESENT IN MEDIASTINAL TISSUE.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

1120 Terminal Sacrifice
Killed on Day : 29
Exposure Group : SD
Animal is signed off from necropsy

Gross Pathology :

LIVER :
LARGE.

No Macroscopic Abnormality Observed :
SPLEEN, BRAIN, MESENTERIC LYMPH NODE, THYMUS, FEMUR/KNEE JOINT, STERNUM, POPLITEAL LYMPH NODE

1120 Continued on the next page ....

Individual Animal Pathology Data

Group: XIB Treatment: 30/0 mg/kg (Recovery) Sex: MALES

Animal Ref	Microscopic & Macroscopic Findings
1120	Continued from previous page

Histopathology :

LIVER :
HYPERTROPHY, PANLOBULAR, HEPATOCELLULAR, severe, with cytoplasmic eosinophilic stippling.
NECROSIS, INDIVIDUAL CELL, INCREASED, minimal.
MITOTIC FIGURES, INCREASED, HEPATOCELLULAR, minimal.
HYPERPLASIA, BILE DUCT, minimal.
SPLEEN :
HEMATOPOIESIS, INCREASED, EXTRAMEDULLARY, minimal.
THYMUS :
DEPLETION/ATROPHY, LYMPHOID, moderate.
CAUSE OF DEATH :
SACRIFICE BY DESIGN.

No Microscopic Abnormality Observed :
BRAIN, MESENTERIC LYMPH NODE, FEMUR/KNEE JOINT, STERNUM, BONE MARROW, LYMPH NODE - POPLITEAL

Appendix L
Individual Total Cell Counts

INDIVIDUAL TOTAL CELL COUNTS

EXPLANATORY NOTES

ABBREVIATIONS:

NP - not taken or not performed

FOOTNOTES:

c Animal was sacrificed *in extremis* prior to this evaluation and tissue was not analyzed.
d Count inadvertently not performed.
e Unable to confirm results.

NOTES:

$$\text{Organ Weight as Percent of Body Weight} = \frac{\text{Organ Weight (g)}}{\text{Final Body Weight (g)}} \times 100$$

$$\text{Total Number of Organ Cells } (\times 10^8) = \frac{\text{Organ Weight (g)}}{\text{Half Organ Weight (g)}} \times \text{Organ Cell Suspension Volume (mL)} \times \text{Number of Cells in Half Organ } (\times 10^6 \text{ cells/mL}) \div 100$$

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells ($x10^8$)
Male, Group I - 0 mg/kg							
101	31.00	0.106	0.3419	0.046	5.5	10.06	1.27
102	34.70	0.110	0.3170	0.052	5.5	7.54	0.88
103	33.40	0.124	0.3713	0.060	5.3	12.04	1.32
104	32.50	0.111	0.3415	0.056	5.2	16.00	1.65
105	33.00	0.091	0.2758	0.050	5.5	10.89	1.09
106	31.20	0.114	0.3654	0.058	5.3	8.86	0.92
107	31.90	0.128	0.4013	0.065	5.4	10.94	1.16
108	30.30	0.107	0.3531	0.056	5.4	8.80	0.91
109	32.70	0.112	0.3425	0.048	5.4	7.37	0.93
110	33.90	0.119	0.3510	0.061	5.5	13.97	1.50
111	32.60	0.145	0.4448	0.077	4.4	25.08	2.08
112	33.90	0.122	0.3599	0.054	5.5	13.42	1.67
113	34.60	0.117	0.3382	0.059	5.0	14.14	1.40
114	33.70	0.115	0.3412	0.061	5.5	13.86	1.44
115	31.50	0.107	0.3397	0.051	5.5	10.78	1.24
116	34.20	0.111	0.3246	0.059	4.5	9.40	0.80
117[a]	NP	NP	NP	NP	NP	NP	NP
118	34.50	0.099	0.2870	0.051	5.4	[b]	[b]
119	34.30	0.152	0.4431	0.076	5.4	13.53	1.46
120	33.50	0.138	0.4119	0.061	5.4	12.60	1.54

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells (x10^8)
Male, Group III - 0.3 mg/kg							
301	35.10	0.150	0.4274	0.070	5.5	14.74	1.74
302	36.10	0.108	0.2992	0.059	5.5	10.94	1.10
303	37.40	0.104	0.2781	0.047	5.5	11.88	1.45
304	37.20	0.188	0.5054	0.085	5.5	14.46	1.76
305	34.50	0.117	0.3391	0.051	5.5	10.18	1.28
306	33.10	0.102	0.3082	0.046	5.3	10.12	1.19
307	31.30	0.095	0.3035	0.049	5.5	11.33	1.21
308	33.70	0.129	0.3828	0.059	5.5	9.62	1.16
309	29.90	0.112	0.3746	0.047	5.3	8.20	1.04
310	32.80	0.130	0.3963	0.063	5.4	6.88	0.77
311	36.60	0.114	0.3115	0.057	5.4	16.34	1.76
312	33.40	0.136	0.4072	0.065	5.5	18.20	2.09
313	31.50	0.076	0.2413	0.043	5.7	6.16	0.62
314	32.20	0.135	0.4193	0.075	5.7	21.84	2.24
315	33.80	0.152	0.4497	0.075	5.6	17.32	1.97
316	31.60	0.099	0.3133	0.045	5.5	7.10	0.86
317	30.20	0.060	0.1987	0.022	5.4	3.02	0.44
318	30.10	0.106	0.3522	0.046	5.5	8.25	1.05
319	30.90	0.060	0.1942	0.023	4.5	5.56	0.65
320	36.70	0.151	0.4114	0.071	6.0	13.20	1.68

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells (x10^8)
Male, Group V - 1 mg/kg							
501	33.30	0.088	0.2643	0.050	5.0	16.50	1.45
502	34.00	0.135	0.3971	0.068	5.5	16.66	1.82
503	33.50	0.090	0.2687	0.048	5.6	7.42	0.78
504	33.30	0.108	0.3243	0.054	5.5	13.26	1.46
505	33.00	0.092	0.2788	0.048	5.4	11.55	1.20
506	35.10	0.115	0.3276	0.058	5.5	12.60	1.37
507	31.30	0.107	0.3419	0.056	5.3	14.08	1.43
508	33.90	0.103	0.3038	0.054	5.3	12.43	1.26
509	33.50	0.112	0.3343	0.049	5.2	13.42	1.60
510	32.30	0.078	0.2415	0.031	5.0	9.02	1.13
511	36.80	0.081	0.2201	0.037	5.0	13.80	1.51
512	36.00	0.118	0.3278	0.055	5.6	10.06	1.21
513	35.90	0.106	0.2953	0.062	5.7	12.16	1.19
514	31.40	0.088	0.2803	0.041	5.7	11.72	1.43
515	35.70	0.124	0.3473	0.059	5.7	11.22	1.34
516	32.10	0.088	0.2741	0.041	5.5	8.08	0.95
517	32.20	0.093	0.2888	0.048	5.6	11.06	1.20
518	35.00	0.114	0.3257	0.054	5.7	13.04	1.57
519	30.70	0.109	0.3550	0.050	5.0	11.55	1.26
520	36.40	0.122	0.3352	0.060	5.8	14.36	1.69

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells (x10^8)
Male, Group VII - 10 mg/kg							
701	31.80	0.078	0.2453	0.040	5.5	11.72	1.26
702	30.90	0.081	0.2621	0.043	5.3	9.18	0.92
703	29.10	0.042	0.1443	0.014	5.0	2.86	0.43
704	28.20	0.053	0.1879	0.027	5.2	5.61	0.57
705	28.40	0.058	0.2042	0.031	5.4	5.17	0.52
706	27.30	0.072	0.2637	0.032	5.5	4.51	0.56
707	24.70	0.054	0.2186	0.023	5.5	3.90	0.50
708	29.70	0.069	0.2323	0.031	5.4	5.39	0.65
709	26.60	0.045	0.1692	0.020	5.1	2.97	0.34
710	27.20	0.076	0.2794	0.034	5.4	5.88	0.71
711	26.80	0.066	0.2463	0.032	5.4	7.15	0.80
712	28.90	0.082	0.2837	0.030	5.0	6.93	0.95
713	31.60	0.083	0.2627	0.040	5.6	8.69	1.01
714	29.60	0.128	0.4324	0.066	6.0	9.79	1.14
715	27.40	0.053	0.1934	0.026	5.4	5.66	0.62
716	27.00	0.052	0.1926	0.024	5.7	4.18	0.52
717	25.20	0.065	0.2579	0.029	5.4	5.78	0.70
718	31.00	0.064	0.2065	0.025	5.5	4.46	0.63
719	30.00	0.054	0.1800	0.028	5.7	4.29	0.47
720	26.90	0.046	0.1710	0.023	5.4	4.29	0.46

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells ($x10^8$)
Male, Group IX - 30 mg/kg							
901	26.20	0.066	0.2519	0.035	5.0	4.78	0.45
902	24.30	0.034	0.1399	0.014	5.5	1.43	0.19
903	23.70	0.021	0.0886	0.016	5.7	3.14	0.23
904	24.20	0.031	0.1281	0.016	5.5	0.82	0.09
905	24.10	0.037	0.1535	0.017	5.5	1.04	0.12
906[a]	NP	NP	NP	NP	NP	NP	NP
907	21.80	0.026	0.1193	0.013	5.5	1.48	0.16
908	25.40	0.037	0.1457	0.034	5.5	3.85	0.23
909	23.50	0.038	0.1617	0.015	5.5	2.36	0.33
910	27.00	0.065	0.2407	0.036	5.5	4.73	0.47
911	25.30	0.042	0.1660	0.020	5.3	1.87	0.21
912	22.00	0.020	0.0909	0.013	5.5	1.92	0.16
913	28.30	0.072	0.2544	0.038	5.7	6.44	0.70
914	28.40	0.082	0.2887	0.036	5.5	9.84	1.23
915	32.40	0.102	0.3148	0.041	5.8	7.04	1.02
916	23.30	0.049	0.2103	0.026	5.5	4.18	0.43
917	29.40	0.068	0.2313	0.032	5.4	5.72	0.66
918	28.00	0.067	0.2393	0.029	5.3	8.08	0.99
919	27.10	0.067	0.2472	0.031	5.2	7.15	0.80
920	29.50	0.068	0.2305	0.033	5.0	7.04	0.73

Individual Total Cell Counts

Animal Number	Final Body Weight (g)	Spleen Weight (g)	Spleen Weight (% Body Weight)	Half Spleen Weight (g)	Spleen Cell Suspension Volume (mL)	Number of Cells in Half Spleen (x 10^6 cells/mL)	Total Number of Spleen Cells (x10^8)
Male, Group XI - 30/0 mg/kg (Recovery)							
1101	31.30	0.091	0.2907	0.046	5.5	7.04	0.77
1102	39.50	0.107	0.2709	0.053	5.5	10.84	1.20
1103	32.20	0.069	0.2143	0.038	5.5	5.56	0.56
1104	30.40	0.086	0.2829	0.044	5.5	10.84	1.17
1105	34.40	0.081	0.2355	0.044	5.5	9.13	0.92
1106	27.20	0.058	0.2132	0.030	5.5	4.02	0.43
1107	27.10	0.060	0.2214	0.028	5.6	5.06	0.61
1108	32.30	0.067	0.2074	0.030	5.5	4.29	0.53
1109	34.70	0.104	0.2997	0.049	5.5	11.33	1.32
1110	24.90	0.091	0.3655	0.044	5.0	8.36	0.86
1111	30.80	0.064	0.2078	0.033	5.5	5.06	0.54
1112[a]	NP	NP	NP	NP	NP	NP	NP
1113	34.70	0.133	0.3833	0.053	5.4	8.96	1.21
1114	30.40	0.048	0.1579	0.026	5.7	2.42	0.25
1115	31.60	0.086	0.2722	0.043	5.5	7.37	0.81
1116	26.90	0.062	0.2305	0.030	5.6	3.63	0.42
1117	27.50	0.072	0.2618	0.039	5.4	4.95	0.49
1118	28.60	0.065	0.2273	0.031	6.0	4.90	0.62
1119	26.20	0.052	0.1985	0.029	5.5	2.36	0.23
1120	28.70	0.055	0.1916	0.024	6.0	[b]	[b]

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group I - 0 mg/kg						
101	0.071	0.2290	0.035	5.5	2.48	0.28
102	0.052	0.1499	0.023	6.0	3.80	0.52
103	0.037	0.1108	0.020	5.5	3.80	0.39
104	0.058	0.1785	0.032	5.5	11.00	1.10
105	0.047	0.1424	0.024	5.5	4.29	0.46
106	0.051	0.1635	0.026	5.5	5.61	0.61
107	0.041	0.1285	0.021	5.5	3.19	0.34
108	0.043	0.1419	0.024	5.5	5.88	0.58
109	0.057	0.1743	0.028	5.5	7.86	0.88
110	0.050	0.1475	0.028	5.8	4.34	0.45
111	0.052	0.1595	0.017	5.5	3.30	0.56
112	0.074	0.2183	0.036	5.7	6.66	0.78
113	0.043	0.1243	0.019	5.0	2.42	0.27
114	0.035	0.1039	0.019	5.4	4.68	0.47
115	0.061	0.1937	0.032	6.0	7.42	0.85
116	0.044	0.1287	0.020	5.4	4.02	0.48
117[a]	NP	NP	NP	NP	NP	NP
118	0.053	0.1536	0.029	5.4	8.36	0.83
119	0.044	0.1283	0.024	5.5	3.85	0.39
120	0.045	0.1343	0.026	5.5	6.93	0.66

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group III - 0.3 mg/kg						
301	0.052	0.1481	0.022	5.5	1.10	0.14
302	0.043	0.1191	0.017	5.5	1.21	0.17
303	0.047	0.1257	0.024	5.5	7.54	0.81
304	0.048	0.1290	0.020	5.5	4.12	0.54
305	0.038	0.1101	0.017	5.5	3.58	0.44
306	0.034	0.1027	0.020	5.5	7.48	0.70
307	0.060	0.1917	0.028	5.5	8.36	0.99
308	0.049	0.1454	0.019	5.4	7.42	1.03
309	0.058	0.1940	0.030	5.5	5.88	0.63
310	0.049	0.1494	0.025	5.5	8.58	0.92
311	0.033	0.0902	0.016	5.0	5.06	0.52
312	0.040	0.1198	0.022	5.5	6.98	0.70
313	0.022	0.0698	0.011	5.4	3.14	0.34
314	0.045	0.1398	0.024	6.0	5.34	0.60
315	0.049	0.1450	0.020	5.5	3.08	0.42
316	0.054	0.1709	0.035	5.3	5.50	0.45
317	0.057	0.1887	0.025	5.5	5.50	0.69
318	0.031	0.1030	0.012	5.0	6.32	0.82
319	0.051	0.1650	0.025	5.4	5.88	0.65
320	0.048	0.1308	0.027	5.0	5.12	0.46

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group V - 1 mg/kg						
501	0.037	0.1111	0.018	5.5	2.58	0.29
502	0.074	0.2176	0.039	5.3	10.67	1.07
503	0.045	0.1343	0.022	5.5	6.00	0.68
504	0.069	0.2072	0.041	5.5	16.00	1.48
505	0.036	0.1091	0.016	5.5	5.34	0.66
506	0.062	0.1766	0.035	5.5	7.59	0.74
507	0.056	0.1789	0.027	5.5	11.44	1.31
508	0.054	0.1593	0.026	5.4	7.81	0.88
509	0.032	0.0955	0.009	5.5	3.02	0.59
510	0.040	0.1238	0.020	5.2	5.17	0.54
511	0.047	0.1277	0.017	5.0	5.83	0.81
512	0.049	0.1361	0.025	5.5	5.34	0.58
513	0.045	0.1253	0.024	5.8	9.74	1.06
514	0.037	0.1178	0.019	5.8	4.84	0.55
515	0.032	0.0896	0.016	5.4	4.90	0.53
516	0.046	0.1433	0.029	5.7	0.38	0.03
517	0.055	0.1708	0.027	5.5	9.35	1.05
518	0.059	0.1686	0.032	6.0	11.22	1.24
519	0.038	0.1238	0.020	5.0	1.38	0.13
520	0.059	0.1621	0.026	5.3	6.16	0.74

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group VII - 10 mg/kg						
701	0.029	0.0912	0.014	5.5	2.80	0.32
702	0.039	0.1262	0.021	5.5	0.72	0.07
703	0.016	0.0550	0.009	5.5	2.48	0.24
704	0.035	0.1241	0.019	5.5	5.06	0.51
705	0.021	0.0739	0.012	5.3	0.55	0.05
706	0.035	0.1282	0.015	5.4	4.51	0.57
707	0.013	0.0526	0.006	5.4	0.11	0.01
708	0.030	0.1010	0.009	5.7	0.82	0.16
709	0.010	0.0376	0.005	5.4	0.16	0.02
710	0.026	0.0956	0.009	5.3	1.54	0.24
711	0.014	0.0522	0.007	5.5	2.20	0.24
712	0.037	0.1280	0.019	5.8	6.71	0.76
713	0.017	0.0538	0.012	5.5	1.26	0.10
714	0.042	0.1419	0.020	5.5	8.08	0.93
715	0.020	0.0730	0.009	5.7	0.00	0.00
716	0.023	0.0852	0.011	5.2	4.24	0.46
717	0.026	0.1032	0.012	5.5	0.94	0.11
718	0.019	0.0613	0.005	5.8	0.22	0.05
719	0.027	0.0900	0.014	5.2	1.21	0.12
720	0.019	0.0706	0.011	5.5	0.06	0.01

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group IX - 30 mg/kg						
901	0.009	0.0344	0.006	5.5	0.06	0.00
902	0.022	0.0905	0.009	5.5	0.06	0.01
903	0.017	0.0717	0.002	5.3	0.00	0.00
904	0.028	0.1157	0.010	5.0	0.06	0.01
905	0.023	0.0954	0.008	5.5	0.00	0.00
906[a]	NP	NP	NP	NP	NP	NP
907	0.015	0.0688	0.006	5.5	0.11	0.02
908	0.065	0.2559	0.013	5.5	0.55	0.15
909	0.009	0.0383	0.003	5.5	0.16	0.03
910	0.027	0.1000	0.009	5.3	0.33	0.05
911	0.016	0.0632	0.008	5.3	0.00	0.00
912	0.014	0.0636	0.009	5.5	0.00	0.00
913	0.025	0.0883	0.016	5.5	0.16	0.01
914	0.030	0.1056	0.018	5.7	3.08	0.29
915	0.039	0.1204	0.019	5.5	3.52	0.40
916	0.023	0.0987	0.011	5.0	0.00	0.00
917	0.039	0.1327	0.019	5.8	4.56	0.54
918	0.029	0.1036	0.014	5.4	1.82	0.20
919	0.026	0.0959	0.013	5.7	1.87	0.21
920	0.014	0.0475	0.006	5.5	0.16	0.02

Individual Total Cell Counts

Animal Number	Thymus Weight (g)	Thymus Weight (% Body Weight)	Half Thymus Weight (g)	Thymus Cell Suspension Volume (mL)	Number of Cells in Half Thymus (x 10^6 cells/mL)	Total Number of Thymus Cells (x10^8)
Male, Group XI - 30/0 mg/kg (Recovery)						
1101	0.027	0.0863	0.012	5.5	0.99	0.12
1102	0.048	0.1215	0.019	5.5	2.75	0.38
1103	0.031	0.0963	0.018	5.5	3.63	0.34
1104	0.028	0.0921	0.016	5.5	0.00	0.00
1105	0.020	0.0581	0.010	5.5	0.82	0.09
1106	0.026	0.0956	0.014	5.5	0.16	0.02
1107	0.018	0.0664	0.012	5.5	0.06	0.00
1108	0.013	0.0402	0.007	5.4	0.00	0.00
1109	0.032	0.0922	0.012	5.0	0.00	0.00
1110	0.014	0.0562	0.006	5.5	0.06	0.01
1111	0.032	0.1039	0.016	5.3	2.42	0.26
1112[a]	NP	NP	NP	NP	NP	NP
1113	0.037	0.1066	0.023	5.5	3.19	0.28
1114	0.045	0.1480	0.023	5.5	0.00	0.00
1115	0.025	0.0791	0.013	5.0	3.52	0.34
1116	0.034	0.1264	0.021	5.0	0.06	0.00
1117	0.023	0.0836	0.014	5.5	0.77	0.07
1118	0.026	0.0909	0.015	5.3	0.50	0.05
1119	0.016	0.0611	0.009	5.2	0.00	0.00
1120	0.020	0.0697	0.011	5.3	[c]	[c]

Appendix M
Electron Microscopy Report from Experimental Pathology Laboratories, Inc.

EPL® Experimental Pathology Laboratories, Inc.

DUPONT/HASKELL LABORATORY

DUPONT STUDY NUMBER: 18318
WORK REQUEST NUMBER: 16160
SERVICE CODE: 1546

AMMONIUM PERFLUOROOCTANOATE: 28-DAY IMMUNOTOXICITY STUDY IN MALE MICE

ELECTRON MICROSCOPY

PATHOLOGY REPORT
EPL PROJECT NO. 129-080

Submitted to:

DuPont/Haskell Laboratory for Health
and Environmental Science
Stine Haskell Research Center
1090 Elkton Road
Newark, DE 19711

Submitted by:

Experimental Pathology Laboratories, Inc.
P.O. Box 12766
Research Triangle Park, NC 27709

October 25, 2006

EPL® Experimental Pathology Laboratories, Inc.

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EPL® Experimental Pathology Laboratories, Inc.

DuPont-18318

DUPONT/HASKELL LABORATORY

DUPONT STUDY NUMBER: 18318
WORK REQUEST NUMBER: 16160
SERVICE CODE: 1546

EPL PROJECT NUMBER 129-080

AMMONIUM PERFLUOROOCTANOATE: 28-DAY IMMUNOTOXICITY STUDY IN MALE MICE

ELECTRON MICROSCOPY

PATHOLOGY SUMMARY

The in-life phase of this study was conducted at Haskell Laboratory for Health and Environmental Sciences, E.I. duPont de Nemours and Company, Newark, Delaware. The objective of this study is to evaluate the potential of ammonium perfluorooctanoate to suppress the primary humoral immune response to sheep red blood cells (SRBC) when administered by oral gavage to male mice for at least 28 days. The table below summarizes the experimental design:

Experimental Design

Group	Number/Group	Daily Dosage (mg/kg)[a]	Dose Solution Concentration (mg/mL)[b]
I	20	0 (Control)	0
III	20	0.3	0.03
V	20	1	0.1
VII	20	10	1
IX	20	30	3
XI	20	30 (Recovery)[c]	3

[a] Weight of test substance/kg of animal body weight.
[b] Solutions will be adjusted for purity (20%)
[c] The recovery group (XI) will be dosed with 30 mg/kg of test substance through test day 23. Following injection of SRBC on test day 24, group XI will be dosed with NANOpure® water, at a volume of 10 mL/kg of body weight, until sacrifice.

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Electron microscopic evaluation of samples of liver from designated animals was added to clarify light microscopic histopathological findings in the liver. Samples of liver from two male mice in Group I (Control) and two male mice in Group V (1mg/kg) that were fixed in formalin were submitted for transmission electron microscopy. The samples that were processed and evaluated are listed in the following table:

TEM Number	Tissue	Animal ID	Group	TEM Negative Number (evaluated)
G06-403	Liver	103	I (Control)	06-1906 to 06-1908
G06-404	Liver	104	I (Control)	06-1909 to 06-1911
G06-405	Liver	503	V (1mg/kg)	06-1912 to 06-1914
G06-406	Liver	504	V (1 mg/kg)	06-1915 to 06-1917

Samples, cut into small cubes, were preserved in formalin and shipped to Experimental Pathology Laboratories, Inc (EPL®), Research Triangle Park, NC. The samples were transferred to the Laboratory for Advanced Electron and Light Optical Methods (LAELOM) at the College of Veterinary Medicine, North Carolina State University, Raleigh, NC for further processing and examination by transmission electron microscopy.

The samples were washed in buffer, post-fixed in 1% osmium tetroxide in the phosphate buffer, dehydrated in an ethanolic series culminating in acetone, and infiltrated with Spurr epoxide resin. The resulting blocks were trimmed and semithin sections (approximately 0.5 μm thick) were cut, mounted on glass slides, and stained with 1% toluidine blue O in 1% sodium borate prior to being examined with a light microscope. The slides of semithin sections were sent to Experimental Pathology Laboratories for evaluation by the Pathologist, Dr. Henry Wall. When the slides were returned to the LAELOM, areas of interest for ultrathin sectioning were trimmed in the corresponding tissue blocks.

Ultrathin (80-90 nm thick) sections were cut from the selected trimmed blocks and placed on 200 mesh copper grids before being stained with uranyl acetate and lead citrate. For each sample, two survey photographs (final print magnification 5,600x) were taken. One higher magnification (final print magnification 22,400x) was taken of each sample to show more cellular detail.

RESULTS

TEM #G06-403 (Animal 103, Control, Liver, TEM Neg # 06-1906 to 06-1908)

Two low magnification images (06-1906 and 06-1907; 5,600X) show portions of adjacent hepatocytes as the primary cell type in the image. Electron-dense areas that are predominantly mitochondria and rough endoplasmic reticulum are separated by intervening areas that contain clustered electron-dense granules against an electron-lucent background. The electron-dense granules are glycogen depositis. A few fat vacuoles that appear as partially electron-lucent smooth contoured vaucuoles, are scattered in the cytoplasm of a few hepatocytes. The higher magnification image (06-1908; 22,400X) shows greater detail of mitochondria, rough endoplasmic reticulum, glycogen deposits, and a few membranous cytoplasmic profiles.

TEM #G06-404 (Animal 104, Control, Liver, TEM Neg # 06-1909 to 06-1911)

The low magnification images (06-1909 and 06-1910; 5,600X) show similar adjacent hepatocytes with electron-dense areas that are primarily mitochondria and endoplasmic reticulum and lighter (less electron-dense) areas with electron-dense granularity. The high magnification image (06-1911; 22,400X) shows the electron-dense granularity to be glycogen deposits. This image also shows greater detail of the mitochondria and rough endoplasmic reticulum that are relatively electron-dense as compared to the glycogen filled areas. All images also show a few smooth contoured lipid vacuoles within hepatocytic cytoplasm. Two deeply electron-dense membrane-bound bodies in the lower right quadrant are considered lysosomes. The core of these bodies have uniform electron-dense granularity compared to the prominent foldings of the cristae in mitochondria.

TEM #G06-405 (Animal 503, Group V/1mg/kg, Liver, TEM Neg # 06-1912 to 06-1914)

Both low magnification images (06-1912 and 06-1913; 5,600X) contain adjacent hepatocytes that have numerous mitochondria rather uniformly distributed in the cytoplasm. Pale granular areas surrounding mitochondria contain glycogen deposits. The glycogen deposits are best detailed in the portion of a hepatocyte in the lower portion of image 06-1913. The higher magnification image (06-1914; 22,400X) shows more detail of mitochondria, lipid vacuoles, glycogen and endoplasmic reticulum. No peroxisomes are clearly defined in the hepatocyte images from this animal.

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TEM #G06-406 (Animal 504, Group V/1mg/kg, Liver, TEM Neg # 06-1915 to 06-1917)

Electron-dense areas that are primarily mitochondria are the predominant feature other than the nucleus in the low magnification images (06-1915 and 06-1916; 5,600X). The paler and granular background is glycogen. A few small smooth-contoured lipid vacuoles are also scattered in a few hepatocytes. The high magnification image (06-1917; 22,400X) shows the detail of mitochondria, rough endoplasmic reticulum, and part of a nucleus. A few lipid vacuoles are also present. No structures that can be clearly defined as peroxisomes are noted.

CONCLUSIONS

At the 1 mg/kg dose of ammonium pefluorooctanoate an increase in peroxisomes was not observed. However, many organelles could not be clearly identified due to poor ultrastructural detail, which was likely the result of formalin fixation. Therefore, definitive conclusions on peroxisomal numbers in treated groups relative to controls could not be drawn.

Henry G. Wall

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25 October 2006
Date

HGW/dc

EPL® Experimental Pathology Laboratories, Inc.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Ammonium Perfluorooctanoate: 28-Day Immunotoxicity Study in Male Mice

Client Study: DuPont-18318; Service Code 1546; Work Request 16160

EPL Project Coordinator: Dr. Henry Wall

EPL Project Number: 129-080

EPL Pathologist: Dr. Henry Wall

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	May 30, 2006	May 30, 2006
Data Review	June 14, 2006	June 14, 2006
Draft Pathology Report	June 27, 2006; July 24, 2006	June 27, 2006; July 24, 2006
Final Pathology Report	October 25, 2006	October 25, 2006

Date reported to Study Director/Management: October 25, 2006

Date of last quarterly facility inspection: October 2006

Jane J. Hollingsworth
EPL Quality Assurance Unit

October 25, 2006
Date

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Form No. 6-2 (October 23, 2006)